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Via Electronic Submission (<http://www.regulations.gov>)

Division of Dockets Management (HFA-305)
Food and Drug Administration
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Re: The Food and Drug Administration Deems Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations Restricting the Sale and Distribution of Tobacco Products and Required Warnings for Tobacco Product Packages and Advertisements; Docket No. FDA-2014-N-0189; RIN 0910-AG38

The American E-Liquid Manufacturing Standards Association (AEMSA) appreciates this opportunity to respond to the Food and Drug Administration's (FDA or Agency) request for comments on the Notice of Proposed Rulemaking (NPRM) for the "Deeming Regulation" (Docket No. FDA-2014-N-0189; RIN 0910-AG38), which proposes to deem currently unregulated tobacco and nicotine-containing products as regulated tobacco products pursuant to the Food, Drug and Cosmetic Act (FDCA), as amended by the Family Smoking Prevention and Tobacco Control Act of 2009 (the Tobacco Control Act).¹ The purpose of this letter is to provide AEMSA's responses to a subset of FDA's requests for comments regarding the potential regulation of electronic cigarettes (e-cigarettes)² and the "e-liquids" used in them. For the reasons set forth below, we believe that FDA has the legal authority to regulate e-cigarettes, including advanced refillable personal vaporizers, and their e-liquid components, differently than tobacco leaf-containing products.

Specifically, FDA should use the enforcement discretion envisioned by Congress and permitted by the statute to establish regulatory requirements tailored to the product types it chooses to deem as regulated tobacco products, including products that only deliver aerosolized

¹ See 79 Fed. Reg. 23142 (April 25, 2014).

² For purposes of this comment, unless otherwise indicated, the term "electronic cigarette" or "e-cigarette" refers to both "cigalike" models as well as advanced refillable personal vaporizers.

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nicotine. We offer several regulatory frameworks for e-cigarettes and e-liquids for FDA to consider, as follows:

1. Based on the extensive existing literature on the safety and public health benefit of e-cigarettes (compared to conventional cigarettes) the Agency should acknowledge that a less rigorous implementation of premarket documentation is appropriate. Specifically, FDA should find that, as a class of products, the availability of e-cigarettes and their e-liquid components are “appropriate for the protection of the public health”. Accordingly, e-cigarette and e-liquid manufacturers should not have to consider the potential population-level impact of their products, but should instead only be required to demonstrate that their products are not unnecessarily harmful to the health of individual consumers by, for example, complying with product standards and Good Manufacturing Practices. FDA should delay the effective date of the Deeming Regulation until it is ready to promulgate industry-specific product standards and GMPs for these products.
2. If FDA chooses to deem e-cigarettes as regulated tobacco products, only the cigarette-look-alike or “cigalike” models and not advanced refillable personal vaporizers (ARPVs) should be considered “covered tobacco products” under the Deeming Regulation, for the same reasons that FDA has suggested exempting premium cigars from regulation under Option 2 of the NPRM. Moreover, the component parts of such products should not be considered covered tobacco products.
3. FDA should use the effective date of the final rule for the Deeming Regulation as the new “Grandfather Date” for e-cigarettes and e-liquid products and model the substantial equivalence requirements for these products based on the Section 510(k) pathway for medical devices.
4. FDA should implement an alternative framework for e-liquid manufacturing companies to comply with Section 904(a)(1) ingredient listing requirement and establish a “master file” system for industry suppliers and component manufacturers to submit confidential information.

We discuss each of these regulatory frameworks, in turn, below, as well as the legal basis supporting the use of FDA’s rulemaking authority to find regulatory solutions other than those explicitly anticipated by Congress and set forth in the statute.

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I. Background on AEMSA

AEMSA is the first and only manufacturers' trade association completely dedicated to creating responsible and sustainable standards for the manufacturing of "e-liquids" used in e-cigarettes. AEMSA is an all-volunteer organization, formed by U.S. manufacturers of e-liquids, to promote safety and responsibility through self-regulation. Our members believe we have a responsibility to self-regulate the e-liquid manufacturing process using professional criteria. One of AEMSA's primary goals is to provide consumers with higher degrees of confidence that our members' products are manufactured with professionalism, accuracy and in a safe manner until such time as FDA promulgates Good Manufacturing Practices for e-liquids. AEMSA has developed manufacturing standards for e-liquids, which may be downloaded from our website at: <http://www.aemsa.org/standards/>. AEMSA supports reasonable, responsible and science-based regulation of e-cigarettes, including advanced refillable personal vaporizers (ARPVs) and the refillable e-liquids used in those products.

We note that although the e-liquid and e-cigarette products manufactured by AEMSA's Member companies may have the corollary benefit of helping smokers quit smoking or nicotine use altogether, these products are not intended to be smoking cessation devices or nicotine replacement therapies (NRTs), but rather recreational use products intended to help adult consumers transition from smoking cigarettes to a less harmful source of nicotine (as compared to cigarettes) that does not involve the heating or combustion of tobacco. As described below, although the available evidence demonstrates that most current "vapers" are using these products as an aid to help them quit or cut down on the use of traditional cigarettes, no claims to this effect are being made by AEMSA Members about their e-liquid or e-cigarette products.

AEMSA is providing these comments to FDA on behalf of its e-liquid manufacturing Members.

II. FDA Should Either Promulgate a New Notice of Proposed Rulemaking to Give the Public an Opportunity to Comment on Regulations Appropriately Tailored to E-Cigarettes and E-Liquids or Reopen the Comment Period for this NPRM Prior to Publishing the Final Rule

While the NPRM for the Deeming Regulation proposes to deem unregulated products and components thereof, including e-cigarettes and e-liquid, as "covered tobacco products" subject to the same regulatory requirements as the currently regulated tobacco products (*e.g.*, cigarettes, cigarette tobacco, smokeless tobacco and roll-your-own tobacco), the proposal is unique in that its *preamble* makes clear that that FDA is still seeking much information regarding e-cigarettes and how such products should be regulated. Specifically, the preamble poses a number of questions regarding how it should regulate newly deemed products, such as:

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- Whether, and, if so, how FDA should consider a different regulatory mechanism for newer proposed deemed tobacco products that cannot, as a practical matter, use the SE pathway.
- Should FDA consider a different compliance policy for proposed deemed tobacco products that cannot, as a practical matter, use the SE pathway? If so, what should the compliance policy entail and would it benefit public health? Instead of, or in addition to, such a policy, should FDA consider ways to expedite the review of some or all premarket applications for proposed deemed products?
- What other FDA actions or regulatory approaches, if any, should FDA consider for proposed deemed tobacco products that are “new tobacco products” under section 910(a)(1) of the FD&C Act and why?

FDA also notes several areas in which the Agency lacks sufficient data regarding e-cigarettes and e-liquids and requests comment on, among other things:

- The effects e-cigarettes and e-liquids have on the public health.
- How e-cigarettes should be regulated based on the continuum of nicotine-delivering products and the potential benefits associated with e-cigarettes.
- The impact of e-cigarettes and e-liquid products either on reducing usage of cigarettes or in possibly prolonging usage of cigarettes while continuing to expose users to the harmful carcinogens in combustible tobacco products.

Inherent in these questions and requests for data is the recognition that there are several novel considerations that must be weighed in determining whether and how to apply the Tobacco Control Act requirements to e-cigarettes and e-liquids – products that Congress never even considered when drafting the legislation. When the Agency is seeking background information to support and inform a regulation in this manner, it typically issues an *Advanced* Notice of Proposed Rulemaking (ANPRM), rather than a NPRM, as FDA did here. ANPRMs, while optional, are promulgated when the Agency needs early public input on key issues before proposing a new rule.

FDA took the ANPRM approach to determine whether it should take steps to regulate menthol in cigarettes.³ In that advanced notice, FDA requested stakeholders to comment on unique regulatory options it might consider with respect to the use of menthol in cigarettes, including potentially establishing tobacco product standards. The advanced notice was designed

³ See Menthol in Cigarettes, Tobacco Products; Request for Comments, Advance Notice of Proposed Rulemaking, 78 Fed. Reg. 44484 (July 24, 2013), <http://www.gpo.gov/fdsys/pkg/FR-2013-07-24/pdf/2013-17805.pdf>.

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to inform the Agency on the available science and data and to help FDA determine what types of studies are needed to address outstanding questions about the public health implications of menthol use in tobacco products. The menthol ANPRM was made available for public comment for a total of 120 days. The Agency is now considering all comments, data, research, and other information submitted to the docket to determine what, if any, regulatory action with respect to menthol in cigarettes is appropriate. If the FDA decides to propose a rule, the next step would be a notice of proposed rulemaking, which would give the public an opportunity to weigh in on the specifics of the proposed rule.

FDA took a much different approach with respect to e-cigarettes, which it included as deemed tobacco products in the NPRM. Even though the Agency makes numerous requests in the preamble for information and data related to the potential impact of these novel products on the public health and how they should be regulated, FDA nevertheless proposed a rule that treats these products as regular tobacco products. As discussed below, we believe that FDA has the legal authority to regulate e-cigarettes and their e-liquid components differently than combustible cigarettes and other tobacco leaf-containing products. Given the available data related to the public health impact of e-cigarettes and, in particular, the growing body of evidence indicating that these products have contributed significantly to the continuing decline in the percentage of the adult population that smokes cigarettes, FDA should have issued an advanced notice before deciding to issue a rule that treats e-cigarettes and combustible cigarettes the same.

As discussed below in Section III, FDA should use its enforcement discretion envisioned by Congress and permitted by the statute to establish regulatory requirements tailored to e-cigarettes and e-liquids. The Agency itself has even tacitly acknowledged that it has such discretion by requesting comments on potential alternative regulatory frameworks for e-cigarettes in the NPRM, and in proposing options not contemplated by Congress. But, because the Agency failed to initially issue an advanced notice, if FDA does tailor the regulatory requirements for e-cigarettes and e-liquids then it must give interested parties an opportunity to comment on such regulations. The Administrative Procedures Act (APA) requires that an agency “give interested persons an opportunity to participate in the rule making through submission of written data, views or arguments....”⁴ Accordingly, given the controversial nature of this proposed rule, FDA should either (1) promulgate a *new* notice of proposed rulemaking that specifically describes how the Agency intends to regulate e-cigarettes and e-liquids or, (2) at the very least, if it chooses to incorporate the tailored e-cigarette requirements in the final version of the current NPRM, reopen the comment period prior to publishing the final rule.

⁴ See 5 U.S.C. § 553(c).

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FDA has previously reopened comment periods for past rulemakings to allow for stakeholder input in advance of implementing regulations. In 1996 the Agency proposed to regulate cigarettes and smokeless tobacco as drugs pursuant to its authority under the FDCA. Several months after closing the 144 day comment period, on March 20, 1996, the Agency published notice of an additional 30 day period to allow for the public to comment on three documents FDA added to the record.⁵ FDA recognized that these additional documents may be part of what the Agency relied upon in making a decision about its jurisdiction over these products, and accordingly reopened the comment period so stakeholders would have a fair shot at responding to these documents. It is, in fact, common practice for FDA to reopen comment periods in order to allow stakeholders to respond to data and information on a specific issue the Agency will rely upon in implementing regulations. Recently, for example, at a June 26, 2014 public meeting on FDA's proposed revisions of the nutrition and supplement facts labels for food,⁶ FDA noted that it was undertaking consumer studies to evaluate the impact of the proposed "added sugars" declaration on consumers and whether this declaration would cause any consumer confusion. FDA assured the stakeholders that once the data from this consumer study was available it would be added to the docket for public comment, although that would likely occur *after* closure of the initial comment period.

FDA should use its enforcement discretion here to establish appropriate regulatory requirements for e-cigarettes and e-liquids and either promulgate a *new* notice of proposed rulemaking to give the public an opportunity to comment on such regulation or, if it chooses to incorporate the tailored e-cigarette requirements in the final version of the current NPRM, it must reopen the comment period prior to publishing the final rule. Doing so will ensure stakeholders have input on the actual regulations, as well as have adequate notice and time to prepare for compliance.

III. E-Cigarette and E-Liquid Products Should Not Be Regulated in the Same Manner as Tobacco Leaf-Containing Products

The NPRM for the Deeming Regulation proposes to deem e-cigarettes, including ARPVs, and their e-liquid components, to be "covered tobacco products" subject to the Tobacco Control Act requirements, which currently only apply to traditional cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco. First and foremost, AEMSA's position is that e-

⁵ See 61 Fed. Reg. 11419 (Mar. 20, 1996).

⁶ See Public Meeting: Proposed Rules on Food Labeling - Revision of the Nutrition and Supplement Facts Labels and Serving Sizes of Foods, <http://www.fda.gov/Food/NewsEvents/WorkshopsMeetingsConferences/ucm398002.htm>.

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cigarettes are technology products, not tobacco products. For purposes of these comments in response to the NPRM, however, we assume, *arguendo*, that e-cigarettes and their e-liquid components will be “covered tobacco products” subject to the Tobacco Control Act requirements, assuming they are used with or contain nicotine derived from tobacco. AEMSA believes that FDA has the legal authority to regulate these products differently than tobacco leaf-containing products. Specifically, we believe that FDA should use the enforcement discretion envisioned by Congress and permitted by the statute to establish regulatory requirements tailored to the product types it chooses to deem as regulated products, including products that only deliver aerosolized nicotine. As Hajek et al. (2014) recently concluded in their review of 81 scientific studies of the health impact and use of electronic cigarettes,⁷ our position is that:

Regulating [electronic cigarettes] as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted on current evidence... Regulatory decisions will provide the greatest public health benefit when they are proportional, based on evidence and incorporate a rational appraisal of likely risks and benefits.

Because e-cigarette and e-liquid products do not contain tobacco leaf but only tobacco-derived substances (*i.e.*, nicotine) these products should *not* be regulated in the same manner as conventional tobacco leaf-containing products (*e.g.*, cigarettes, smokeless tobacco, roll-your-own tobacco, and currently unregulated products such as cigars, hookah and pipe tobacco). Rather, FDA should use the enforcement discretion envisioned by Congress and permitted by the statute to establish regulatory requirements tailored to the tobacco product types it chooses to deem as regulated products, including products that only deliver aerosolized nicotine. In other words, FDA should use its rulemaking authority to find regulatory solutions other than those explicitly anticipated by Congress and set forth in the statute. We propose potential regulatory frameworks for e-cigarettes and e-liquids in Section IV below that are more appropriately suited to the lesser risks posed by these non-tobacco leaf product forms.

a. Congress Intended FDA to Use its Discretion to Establish Appropriate Regulatory Requirements for Tobacco Products Deemed to be Regulated by the NPRM and Not to Strictly Apply the Tobacco Control Act Requirements to All Deemed Products

There is ample statutory authority to support the view that Congress did not intend FDA to rigidly apply the Tobacco Control Act requirements to those deemed tobacco products that do not contain actual tobacco leaf. Instead of requiring a “one-size-fits-all” approach for all tobacco

⁷ See Hajek, P. et al. (2014). Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction*. doi:10.1111/add.12659.

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products, whether or not they contain tobacco leaf, the statute leaves room for the Agency to tailor the regulatory requirements for each “other” tobacco product category that it chooses to regulate. This is because although a “tobacco product” is defined broadly, in pertinent part, as anything made or *derived* from tobacco, the statute only provided FDA with immediate authority to regulate certain types of tobacco products, all of which contain tobacco leaf: cigarettes, cigarette tobacco, roll-your-own tobacco and smokeless tobacco. Of course, the statute further provides the Agency with the discretion to “deem” other tobacco product types to be similarly regulated, if it so chooses. Specifically, Section 901(b) of the Act states what types of tobacco products the law will apply to: “[Chapter IX of the FDCA] shall apply to all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco and to any other tobacco products that the Secretary [of Health and Human Services] by regulation deems to be subject to [Chapter IX of the FDCA].”⁸ But simply stating that the other tobacco products that FDA chooses to regulate would be subject to the new tobacco chapter of the FDCA does not mean that all of the specific requirements designed for products that contain tobacco leaf need to be rigidly applied to products that do *not* contain tobacco leaf.

To support this concept, we note that in providing FDA with the discretion to deem (or *not* to deem) other types of tobacco products to be *regulated* tobacco products via its rulemaking authority, Congress clearly anticipated that FDA would use its expertise to determine which other tobacco product categories to regulate. Put simply, Congress gave FDA the ability to *not* regulate other tobacco product categories if it determined that such regulation was unnecessary. Indeed, as discussed below, FDA has acknowledged the right to exercise this discretion in the proposed “Option 2” of the NPRM, whereby “premium cigars” – a combustible product with known health consequences – would be exempted from the Tobacco Control Act requirements.

But there is also nothing in the statute or its legislative history to indicate that Congress envisioned FDA’s enforcement discretion to end with being able to choose which other tobacco products to regulate. On the contrary, Section 3 of the Tobacco Control Act sets out the purpose of the legislation and provides the only statutory guidance as to what standard should apply to FDA’s exercise of discretion. Specifically, Section 3(4) of the Act notes that one of the primary purposes of the law is “to provide new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry’s efforts to develop, introduce, and promote less harmful tobacco products[.]” Considering this in light of Section 701(a) of the FDCA, which provides the Agency with “[t]he authority to promulgate regulations for the efficient

⁸ See 21 U.S.C.A. § 387 (2010). A review of the legislative history of this provision did not provide any specific insight into what types of products Congress intended to capture with the phrase “any other tobacco products.” This language has been used in every tobacco product bill introduced since the 105th Congress in 1998.

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enforcement” of the law, it is clear that the fact that Congress even gave FDA the ability to choose *which* other tobacco products to regulate suggests that it also intended the Agency to use its discretion to impose appropriate regulatory requirements tailored to the tobacco product types that it did choose to deem as subject to the Act. As noted above, the Agency itself has tacitly acknowledged that it has such discretion by requesting comments on potential alternative regulatory frameworks for e-cigarettes in the NPRM.

For the reasons discussed below, we think that Congress intended the specific statutory requirements in the Tobacco Control Act that currently apply to cigarettes, cigarette tobacco, smokeless tobacco and roll-your-own tobacco to apply to the deemed products that also contain tobacco leaf (*e.g.*, cigars, pipe tobacco, hookah tobacco, etc.), but not necessarily to the deemed products that only contain tobacco-derived substances, like e-cigarettes and e-liquid that contain nicotine derived from tobacco. Rigidly applying those same statutory requirements to products with significantly different harm profiles simply does not make sense. By not explicitly stating that all deemed products must be subjected to the same regulatory requirements as tobacco leaf-containing products, for those novel deemed products that are demonstrably less harmful, the statute provides FDA with enough leeway to establish appropriate regulatory procedures that are commensurate with the harm that requires regulation.

i. Neither the Tobacco Control Act’s Plain Language Nor its Legislative History Strictly Require FDA to Apply All of the Tobacco Control Act Requirements to All Deemed Products

The plain language of the statute indicates that Congress only intended the Tobacco Control Act requirements, as enacted, to be strictly applied to products that actually contain tobacco leaf, and not necessarily to products that only contain tobacco-derived substances. We note that many of the provisions of the Act only apply to specific product types, all of which contain tobacco-leaf. For example:

- Section 102 of the Tobacco Control Act required FDA to reissue the Agency’s 1996 final rule on cigarette and smokeless tobacco (with certain exceptions). That rule, which is now codified in 21 C.F.R. Part 1140, specifically prohibits the sale of cigarettes and smokeless tobacco to individuals under the age of 18 and imposes specific marketing, labeling, and advertising requirements. We further note that nothing in FDA’s lengthy rulemaking from the 1990’s indicates that, at that time, the Agency ever contemplated

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asserting authority over tobacco products other than cigarettes and smokeless tobacco, much less products that do not contain tobacco leaf.⁹

- Sections 201 and 202 of the Tobacco Control Act amended the Federal Cigarette Labeling and Advertising Act (FLCAA)¹⁰ and Comprehensive Smokeless Tobacco Health Education Act (CSTHEA)¹¹, respectively, to transfer authority over cigarette and smokeless tobacco labeling and advertising warnings from the Federal Trade Commission to FDA. Importantly, FLCAA and CSTHEA both require specific warning language to appear on the packaging of cigarettes and smokeless tobacco products respectively. This is yet another indication that Congress did not intend a one-size-fits-all approach to regulation of tobacco products. Congress anticipated consideration of the unique risks posed by each type of tobacco product when making regulatory determinations. The warning labels enacted by these statutes reflect the unique risks posed by the different types of tobacco products, *i.e.*, the higher risks of mouth cancer and gum disease posed by smokeless tobacco products, and the presence of carbon monoxide in cigarette smoke.
- Section 907(a)(1)(A) sets forth a tobacco product standard that specifically prohibits the use of characterizing flavors (other than menthol) in conventional cigarettes only. Tobacco leaf-containing products are also the only types of tobacco products that Congress envisioned would be subject to user fees. Specifically, even though cigars and pipe tobacco are not yet otherwise regulated by FDA, Section 919 of the Act states that user fees will be allocated among manufacturers and importers of cigarettes, cigars, snuff, chewing tobacco, pipe tobacco and roll-your-own tobacco. There is no mention in the statute or its legislative history of any other tobacco or tobacco-derived products with respect to user fees.

Even with respect to the non-specific provisions in the Act (*i.e.*, the provisions that are intended to apply to *all* tobacco products), the statute implies that Congress only intended those requirements to be strictly applied to tobacco products that actually contain tobacco leaf and,

⁹ Of course, the Agency had no need to mention other nicotine delivery forms in its proposed regulations at this time, as it was successfully intimidating all that tried to introduce other nicotine forms that they needed to be regulated as drugs. See footnote 52 below regarding FDA's response to the introduction of the FAVOR® smokeless cigarette in the 1980s.

¹⁰ See 15 U.S.C. §§ 1331–1341.

¹¹ See 15 U.S.C. §§ 4401–4408.

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thus, not necessarily to deemed products that *only* contain tobacco-derived substances. For example, although Section 904 (“Submission of Health Information to the Secretary”) generally applies to “tobacco product manufacturers,” it is clear that Congress only had tobacco leaf-containing products in mind when it described the ingredient listing requirement to include ingredients added to the “tobacco, paper, filter” or other parts of each tobacco product.¹² There is no mention of “liquid,” “vapor,” “aerosol” or other terms associated with e-cigarettes. Even for the harmful and potentially harmful constituents (HPHC) disclosure requirement in Section 904(a)(3), the statute specifically notes that such constituents include “smoke constituents,” which can only be generated by combusting tobacco leaf, and makes no mention of “aerosol” or “vapor” constituents generated by e-cigarettes.¹³ Furthermore, regarding the requirement that tobacco products be manufactured in accordance with Good Manufacturing Practices, as promulgated by FDA, we note that Section 906(e) provides that such practices “may differ based on the type of tobacco product involved.”

It is quite apparent from reading the statute that Congress only contemplated tobacco leaf-containing products would be subject to the requirements as enacted.

ii. There is No Mention of E-Cigarettes or E-Liquid in the Tobacco Control Act or its Legislative History

This is further supported by the fact that neither e-cigarettes nor e-liquid are mentioned anywhere in the Tobacco Control Act or its legislative history. As noted above, FDA exercised its discretion to *not* deem premium cigars as covered tobacco products in its proposed “Option 2” of the NPRM. In a recent draft report by the House Appropriations Committee on the FDA funding bill, the Committee noted that exempting premium cigars from the scope of the Deeming Regulation made sense because there was “little mention of cigars” in the legislation. Specifically, the Committee stated¹⁴:

¹² See Section 904(a)(1).

¹³ FDA’s Guidance Document for HPHC testing also makes clear that a “one-size-fits-all” approach does not make sense for tobacco products. In that guidance, the Agency distinguishes between the different types of regulated tobacco products and which of the 93 HPHCs need to be tested for each product type (*i.e.*, smokeless tobacco companies are not required to test for HPHCs such as carbon monoxide that result from combusting tobacco). See <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297828.pdf>.

¹⁴ See <http://appropriations.house.gov/uploadedfiles/hrpt-113-hr-fy2015-agriculture.pdf>.

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Deeming Regulations.—The Committee is encouraged that FDA has provided options for a way forward on distinguishing between premium cigars and other tobacco products in its recently proposed rule “Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products” (Docket No. FDA–2014–N–0189). In particular, the Committee notes that FDA is considering excluding premium cigars from the scope of this proposed rule through Option 2. The Committee believes this could be a viable solution, given that the Family Smoking Prevention and Tobacco Control Act makes little mention of cigars throughout the legislation, and there is even less evidence that Congress intended to focus on the unique subset of premium cigars. The Committee notes that premium cigars are shown to be distinct from other tobacco products in their effects on youth initiation, the frequency of their use by youth and young adults, and other such behavioral and economic factors.

While there may be “little mention” of cigars in the Tobacco Control Act, there is no mention at all of e-cigarettes or e-liquids in either the text of the legislation or in the Congressional record. These products, which are clearly distinct from the currently regulated tobacco leaf-containing products, were not on the U.S. market or were just entering the market when the Tobacco Control Act was being debated, and Congress was clearly unaware of their existence. This further suggests that Congress could not have intended FDA to strictly apply the Tobacco Control Act requirements to these novel, tobacco leaf-free products.

iii. There are Numerous Examples of FDA Using its Rulemaking Authority to Implement Appropriate Regulatory Solutions Other Than Those Anticipated by Explicit Language in the FDCA

It is important to understand that the Tobacco Control Act is not a standalone piece of legislation, but amended the FDCA – a statute with a rich history, and one that FDA has always interpreted as providing it with much rulemaking and enforcement flexibility. Indeed, there are numerous examples of FDA using its rulemaking authority to find ways around strictures in the statute. As noted above, Section 701(a) of the statute gives the Agency the authority to promulgate substantive rules that will provide for the “efficient enforcement” of the Act. Specific examples of FDA’s use of this enforcement discretion are provided below.

1. Section 404 Emergency Permit Controls

One such example is the requirement in Section 404 of the FDCA for emergency permit controls. This statutory provision effectively allows FDA to prohibit the interstate shipment of certain types of food (*i.e.*, classes of food found by FDA to be injurious to the public health when

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contaminated with micro-organisms, but for which there are no adequate means to determine whether or not the foods are in fact injurious due to microbial contamination prior to their interstate shipment), unless such food processors have obtained an emergency permit from the Agency. Section 404 requires FDA to promulgate regulations providing for the issuance of such permits, which FDA did in 21 C.F.R. Part 108. The procedures set out in subpart A of Part 108, however, are quite burdensome.¹⁵ Realizing that applying these requirements to certain classes of food would go against the Agency's Section 701(a) mandate to provide for the efficient enforcement of the Act, FDA created an exemption process from the need for a permit in the regulations. Specifically, FDA promulgated regulations in 21 C.F.R. §§ 108.25 and 108.35 exempting acidified foods and thermally processed low-acid foods in hermetically sealed containers, respectively, from the permit requirement, even though the inadequate or improper manufacturing, processing or packing of these foods "may result in the distribution in interstate commerce of processed foods that may be injurious to health." Rather than simply requiring processors of such foods to obtain an emergency permit, as required by the statute, FDA took the initiative to exempt those food processors from this obligation, provided the requirements set forth in the regulations are met.¹⁶

This exemption process promptly became the status quo within the part of the food industry engaged in canning and packaging of acidified foods. The exemption requires food manufacturers to provide information that FDA did not have the authority to mandate otherwise as part of the permit application process, *i.e.*, register the facility, allow access to records during inspections (Section 404(c)), submit process details and provide a certification regarding the adequacy of the process to control microorganisms. In other words, the mandatory requirements for the exemption required companies to do certain things that provided FDA with confidence regarding the safety of the processed food, and obviated the need for the Agency to go through the burden of issuing and managing permits for individual facilities. In short, FDA effectively used its rulemaking authority to implement appropriate regulatory solutions other than those explicitly anticipated by Section 404 of the FDCA.

¹⁵ Specifically, subpart A of Part 108 establishes the procedures for, among other things, determining and revoking the need for a permit, issuing or denying a permit, and suspending and reinstating a permit.

¹⁶ Of course, should a processor fail to meet any of these regulatory requirements, such failure "shall constitute a *prima facie* basis for immediate application of the emergency permit control provisions of section 404[.]" See 21 C.F.R. § 108.19(b).

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2. FDA's Constituents Policy and Threshold of Regulation Rule for Food Additives

Another example of how FDA used its rulemaking authority to find regulatory solutions other than those explicitly anticipated by Congress can be seen in the regulatory framework established to distinguish food additives from *constituents* of food additives. Section 409(c)(3)(A) of the FDCA, which is known as the “Delaney Clause,” prohibits FDA from clearing the use of a food additive that has been shown to be carcinogenic. The Delaney Clause was initially enacted in 1958 as part of the Food Additives Amendment, and states that:

[N]o such regulation [authorizing use of a food additive] shall issue if a fair evaluation of the data before the Secretary . . . fails to establish that the proposed use of the food additive, under the conditions of use specified in the regulation, will be safe: *Provided*, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . .

When the Food Additives Amendment was passed, little was known about the carcinogenic propensities of a wide variety of additives. Following the enactment of the Delaney Clause, many substances were shown to be potentially carcinogenic because of their chemical constituents. In 1982, the FDA responded to this trend by issuing an advanced notice of proposed rulemaking proposing that a food additive would not be denied approval under the Delaney Clause unless the additive itself, and not just the constituent chemicals used to make it, was shown to cause cancer.¹⁷ More specifically, under this “Constituents Policy,” FDA distinguishes between an additive as a whole and its constituents. If an additive as a whole is not

¹⁷ See FDA Policy for Regulating Carcinogenic Chemicals in Food and Color Additives, 47 Fed. Reg. 14,464 (April 2, 1982). In a November 26, 2004 *Federal Register* notice (69 Fed. Reg. 68831, 68836), FDA withdrew this advance notice of proposed rulemaking (ANPR) along with approximately 80 other proposed actions and rules that were no longer considered viable candidates for final action. The withdrawal represents an effort by the Agency to reduce its regulatory backlog and focus its resources on current public health issues. The notice states that, “withdrawal of a proposal is not intended to affect whatever utility the preamble statements may currently have as indications of FDA’s position on a matter at the time the proposal was published,” and further that, “in some cases the preambles of these proposals may still reflect the current position of FDA on the matter addressed.” Thus, despite the Agency’s withdrawal of the ANPR, the Constituents Policy outlined in the April 2, 1982 *Federal Register* notice remains a valid policy by which to evaluate minor carcinogenic constituents of food additives.

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carcinogenic, the presence of unavoidable low levels of carcinogenic constituents does *not* automatically trigger the Delaney Clause, barring the use of the additive. Instead, the safety of the additive may be evaluated under the general safety provisions of the Act.

Despite the explicit language in the Delaney Clause prohibiting carcinogenic food additives, FDA developed this Constituents Policy as means of dealing rationally with food additives that clearly present no meaningful toxicological risk, but that may contain minute levels of carcinogenic impurities or carcinogenic residual starting materials.¹⁸

FDA promulgated a similar regulatory solution beyond the scope of the explicit language in the FDCA with its Threshold of Regulation rule for substances used in food-contact articles. A “food additive” is defined in Section 201(s) of the Act, in pertinent part, as any substance the intended use of which results, or reasonably expected to result, in its becoming a component of food, unless the substance is generally recognized as safe (GRAS) or subject to a prior sanction. With respect to food-contact materials, such substances may also be food additives if they migrate from the packaging to become a component of the food. Under Section 409 of the Act, a substance that falls within the statutory definition of a food additive must be the subject of an applicable food additive regulation. In 1997, the Food and Drug Administration Modernization Act (FDAMA) amended Section 409 of the FDCA to establish a food contact notification (FCN) process that allows for faster review of food-contact substances that are also food additives. Prior to the establishment of the FCN program in the legislation, however, FDA used its rulemaking authority to establish a regulatory solution for food-contact materials that also fell within the food additive definition.

Specifically, FDA promulgated its “Threshold of Regulation” rule in 21 C.F.R. § 170.39 to enable the Agency to, on a case-by-case basis, exempt substances used in contact with food (that migrate or that may be expected to migrate from the packaging to the food) from regulation as food additives if such substances have not been shown to be carcinogens, do not possess molecular structures suggestive of carcinogenicity, and the dietary exposures to the substances do not exceed 0.5 parts per billion (ppb) or 1% of the acceptable daily intake (ADI) if the substances are regulated as direct food additives. This means that if the anticipated dietary exposure to a substance is sufficiently low, and the molecular structure of that substance does not have features that give cause for safety concerns, FDA permits the use of that substance in contact with food pursuant to its Threshold of Regulation rule, even though the FDCA might otherwise have required petitioning a food additive regulation for the substance.

¹⁸ The use of the Constituents Policy as a means of avoiding application of the Delaney Clause when appropriate has been judicially upheld. *See Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984).

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3. FDA Has Exercised Discretion When Implementing Certain Tobacco Control Act Requirements

FDA has even displayed a willingness to exercise enforcement discretion with respect to implementing the Tobacco Control Act. For example, despite the explicit statutory requirement, the Agency has stated that it will not enforce the premarket substantial equivalence requirements for certain types of modifications made to grandfathered tobacco products that are not expected to affect the public health profile of the product. Specifically, Section 905(j) Substantial Equivalence Reports do not need to be submitted for the following product modifications:

- Certain label and packaging changes as follows: (1) removal of the descriptors “light,” “mild,” or “low” in compliance with the Act, (2) inclusion of any required graphic warnings, (3) package type modifications (*i.e.*, hard to soft pack or vice versa), provided such change did not modify the tobacco product in any other way (*e.g.*, a change in moisture content, shelf life, ingredient composition, nicotine delivery, harmful/potentially harmful constituents), and (4) changes made to font size, ink color, or background color of the packaging or labels.¹⁹
- When a new supplier is used for the same additive with identical specifications;²⁰ and
- Tobacco blending changes required to address the natural variation of tobacco in order to maintain a consistent product.²¹

FDA has also exercised similar discretion in not fully enforcing the Section 904(a)(3) requirement for tobacco product manufacturers to report the amount of HPHCs in their products. Specifically, the Agency has published guidance stating that it would, for now, only require the submission of data on only 20 of the 93 substances that the Agency has identified as HPHCs. FDA justified this decision in terms of both expediency and practicality, as the Agency’s ability

¹⁹ See *FDA Draft Guidance for Industry and FDA Staff: Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions*, 76 Fed. Reg. 55,927 (September 9, 2011), available at: <http://www.fda.gov/downloads/TobaccoProducts/ResourcesforYou/ForIndustry/UCM271239.pdf>.

²⁰ *Id.* at 6.

²¹ *Id.* at 8.

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to achieve the public health goals of the legislation will depend largely on whether it can efficiently utilize its resources.²²

These are just a few of the examples of FDA effectively using its rulemaking authority to implement regulatory solutions other than those explicitly anticipated by the legislation. The Agency should take a similar approach with how it treats e-cigarette and e-liquid products in the Deeming Regulation by exempting these novel products from specific requirements in the Tobacco Control Act that are clearly designed and intended to apply to tobacco leaf-containing products, such as the premarket authorization requirement to demonstrate a net positive population-level impact for new products. Of course, manufacturers would still be required to demonstrate that their products are “appropriate for the protection of the public health,” but by focusing solely on the impact of their product on the health of the *individual* consumer. This and other potential regulatory solutions are described in Section IV below.

iv. Strictly Applying the Tobacco Control Act’s Requirements to E-Cigarettes and E-Liquid Products Would Result in the Vast Majority of these Products Being Removed from the Market Which Will be Tantamount to a Ban Which Congress Did Not Intend

Rigidly applying the same regulatory requirements to e-cigarettes and e-liquids that currently only apply to tobacco leaf-containing products would mean that, in order to meet the “appropriate for the protection of the public health” standard to market such products, manufacturers would have to demonstrate that each of their individual products will not have an adverse impact on the net-population “public” health (*i.e.*, overall tobacco-use initiation and cessation rates).²³ For the reasons discussed below, placing this high burden on manufacturers of

²² See *FDA Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the FDCA*, 77 Fed. Reg. 20030 at 3 (April 3, 2012), available online at: <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297828.pdf>.

²³ Specifically, Section 910(c)(4) of the Act provides that “the finding as to whether the marketing of a tobacco product for which [a Premarket Tobacco Product Application] has been submitted is appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account – (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will starting using such products.”

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nicotine-only products that have the ability to help smokers transition to less harmful forms of recreational nicotine will result in most, and possibly all, such products being removed from the market. It would also make it prohibitively difficult for any such new products to enter the market, which would be tantamount to a ban, despite Congress's clear commitment to allow the marketing of potentially reduced risk products. Instead, FDA should use the discretion envisioned by Congress and permitted by the statute to establish alternative regulatory frameworks for such deemed products.²⁴

1. Size of the E-Liquid Industry

To understand the real-world impact of strictly applying the Tobacco Control Act requirements to this new industry, the Agency must first recognize the number of small businesses that will be affected. In the proposed rule, the Agency grossly underestimated both the number of companies in the "other tobacco, e-cigarettes, and nicotine product" category, as well as the number of such products on the market. More specifically, FDA has estimated that only 140 "other tobacco, e-cigarettes, and nicotine product manufacturers" will register as tobacco product establishments pursuant to Sections 905 and that 188 companies will submit their product and ingredient lists to the Agency pursuant to Section 904 of the Act. FDA has also grossly underestimated that it will only receive 25 Premarket Tobacco Product Applications (PMTAs) for new products.

These estimates are off by orders of magnitude, as the e-cigarette industry in the U.S. has roughly doubled *every year* since the products first started being commercially distributed.²⁵

²⁴ Potential alternative frameworks for these novel products are discussed in Section IV below.

²⁵ We note, however that these gross underestimates are not miscalculations on FDA's part, but rather based on the assumption that most of these small companies will not be able to comply with the burdensome and costly regulations, and thus will be forced to exit the industry. FDA's own *Regulatory Impact Analysis* for the proposed rule acknowledges that the regulatory burdens of the rule will result in most companies exiting the industry, but failed to estimate the value of this loss of consumer choice. *See* <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/UCM394933.pdf>. Specifically, FDA states in the impact analysis that

In addition, we assume that the per-product (or per-UPC) costs of this proposed rule, including labeling changes and premarket tobacco product applications (PMTAs) are costly, and if there are no valid predicate products for substantial equivalence submissions, electronic cigarettes would

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Sales in 2008 were approximately \$50 million; in 2014 sales are expected to exceed well over \$1 billion.²⁶ That value, however, may underestimate the actual size of the e-cigarette industry because it is based on limited monitoring of major sales outlets (*e.g.*, convenience stores), which mainly report sales of cigalike e-cigarette products captured from electronic sales records. Not included in this data are sales from the rapidly growing e-cigarette subcategory of ARPVs and their components (*e.g.*, e-liquids and hardware), that are sold either online or in brick-and-mortar “vape shops”. Considering ARPV and e-liquid sales, total e-cigarette sales in the U.S. are expected to be between \$2.2 to 3 billion in 2014.²⁷

With respect to the refillable e-liquid industry alone, the available evidence indicates that there are at least **5,000** and possibly up to **15,000** individual manufacturers and retailers

(...continued)

necessarily be marketed through the premarket tobacco application pathway. There are currently a large number of electronic cigarette products being marketed, some of which have very little market share while others represent product variation among larger market players. Products that do not have sufficient sales to justify incurring the costs of complying with the proposed rule would exit. Products with larger sales will more likely bear these costs to come into compliance with any final rule, but we expect some reduction in the variety of products offered even among larger players. Therefore, we expect that considerable product consolidation and exit would occur, as well as the entry, exit, and consolidation that would be expected to occur in an emerging market and that would occur under baseline conditions.

We note, however, that while many of these companies are small, they are entrepreneurial and are continuing to grow, and intend to comply with FDA’s regulations. To propose a rule that assumes up to 99.99% of the thriving ARPV and e-liquid manufacturing companies will be eliminated is obdurate beyond reason. Rather, FDA should use the enforcement discretion envisioned by Congress to implement appropriate regulatory requirements tailored to these products, as discussed in Section IV.

²⁶ See Nicotine Science and Policy, “New Estimates Double Size of E-Cigarette Market; Increasing Importance of Refillable and Modified Devices” by G. Stimson (March 2014); available online at: <http://nicotinepolicy.net/gerry-stimson/1317-wells-fargo-march-2014>.

²⁷ See Wells Fargo Securities, Equity Research, March 24, 2014, “Tobacco Talk: Vapors/Tanks Driving Next Wave of E-E-Vapor Growth,” available online at: http://www.vaporworldexpo.com/PDFs/Tobacco_Talk_Vapors_Tanks_%20March%202014.pdf.

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producing e-liquid products in the U.S., nearly all of which are small businesses (*i.e.*, less than 350 employees), including vape shops that mix their own products. Specifically, we note that:

- The Smoke Free Alternatives Trade Association, a trade association of representing small and mid-sized businesses in the vapor industry, including vape shops, manufacturers, importers and distributors, has estimated that there are 1,200 e-liquid manufacturers that make their own e-liquid and 15,000 vape shops in the United States (many of whom also mix their own e-liquids), representing over 65,000 jobs. This estimate is based on internal data collected from manufacturer and distributor members, as well as insurance researchers. *See* www.sfata.org.
- Prominent Wall Street Securities Analyst Bonnie Herzog of Wells Fargo estimates that that are 5,000 to 10,000 vape shops in the United States.²⁸
- The Vapor Search USA online portal, available at <http://www.vaporsearchusa.com/>, has over 5,000 e-liquid producers throughout the United States listed in its database.
- The Electronic Cigarette Forum (ECF), an online community for e-cigarette consumers and stakeholders (available at <http://www.e-cigarette-forum.com/forum/>) has nearly 1,700 e-cigarette and e-liquid businesses (including U.S.-based manufacturers and foreign importers) on record.²⁹
- Another potential method of determining the size of the e-liquid market is to calculate the total amount of nicotine being consumed in the country from e-liquids by taking the total amount of USP grade nicotine produced/imported into the country and discounting the amount used in nicotine replacement therapies (NRTs). Based on this and using the average nicotine concentration in e-liquid (of 1.8% or 18 mg/mL), the total volume of nicotine-containing e-liquid consumed in the U.S. may be extrapolated.

These estimates are only for the e-liquid industry, and do not include the hundreds, if not *thousands*, of companies that are manufacturing the various hardware components used in ARPVs (*i.e.*, “mod” components including adapters, atomizers, cartomizers, clearomizers, batteries, chargers, tanks, endcaps, tubing, internal microprocessors/motherboards, springs, o-

²⁸ *See* Wells Fargo Securities, Equity Research, April 14, 2014, “Vape Shops – Springing Up Across The Country,” available online at: http://www.vaporworldexpo.com/PDFs/Tobacco_%20Vape_Shop_Visit_Apri_2014.pdf.

²⁹ Only those who apply and pay for recognized vendor status on ECF are listed here.

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rings, drip-tips/mouth pieces, wicking materials, and other device components such as internal connectors, buttons, casings, gaskets, seals, internal charging circuitry components, etc.).³⁰ If the NPRM becomes effective as drafted, all of these thousands of companies could fall within meaning of “covered tobacco product” manufacturers.

2. Tantamount Ban of E-Cigarettes

Strictly applying all of the Tobacco Control Act requirements to e-cigarette and e-liquid products would effectively result in a ban of such products, which would clearly be contrary to Congressional intent, as described below. First, because there are no viable predicate products that were on the market on the February 15, 2007 “grandfather date,” no e-cigarette or e-liquid products on the market today will be able to demonstrate substantial equivalence (SE) to a grandfathered product (unless the Agency utilizes a more appropriate grandfather date for these novel products, as suggested in Section IV below). This means that, if the NPRM becomes effective, all current and new e-cigarette and e-liquid products will need to go through the Premarket Tobacco Application (PMTA) process outlined in Section 910 of the Act.³¹

The data required to support a PMTA are extensive and must include a detailed description of the “components, ingredients, additives, and properties” of the product, and information regarding methods and facilities used for production³² to “full reports of all investigations of health risks (including studies submitted to support [a] showing that the tobacco product is appropriate for the protection of the public health...)”³³ Moreover, in order to meet the high “appropriate for the protection of the public health” legal standard to market a new

³⁰ Further, each of these components can come in many models, sizes or be made from different raw materials.

³¹ In the NPRM, FDA has proposed a compliance policy that would delay enforcement of the premarket authorization requirements for two years for the newly deemed products. Under this policy, FDA would allow any product marketed between February 15, 2007 and two years after the *effective date* of the Deeming Regulation to remain on the market until such time as the FDA denies the SE or PMTA submission (that must be submitted by the two year anniversary of the effective date of the regulation).

³² 21 U.S.C. § 387j.

³³ See *FDA Draft Guidance for Industry: Applications for Premarket Review of New Tobacco Products*, 76 Fed. Reg. 60,055 at 7 (September 28, 2011), available online at: <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM273425.pdf>.

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product, e-cigarette and e-liquid manufacturers must consider the potential risks and benefits that their product will have on the population as a whole, including users and nonusers of the tobacco product, and taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products (cessation), as well as the increased or decreased likelihood that those who do not currently use tobacco products will start using such products (initiation). Put simply, the statute places the burden on manufacturers to show that each of their products will *not* have an adverse impact on the net-population “public” health (*i.e.*, overall tobacco-use initiation and cessation rates). An application that fails to demonstrate that permitting the new product to be marketed would be appropriate for the protection of the public health shall be denied by FDA pursuant to Section 910(c)(2) of the Tobacco Control Act.

Even if it were possible to meet this standard, which no tobacco company has yet been able to do, the amount and type of data that would be required would make it impossible for any single e-cigarette or e-liquid company to develop on its own. FDA has published a draft Guidance for Industry on the type of data that would be required for “Applications for Premarket Review of New Tobacco Products.”³⁴ In that guidance document, the Agency makes clear that “non-clinical studies alone generally are not sufficient to support a determination that the product is appropriate for the protection of public health,” and that a combination of, among other things, laboratory analyses, pre-clinical toxicity data, clinical studies, epidemiologic evidence, consumer perception data, mathematical models, abuse liability data and long-term *post*-market surveillance data would be needed to meet the high standard. It will not be possible for manufacturers of novel products such as e-cigarettes and e-liquids to develop the data necessary to meet this standard. As such, placing the “public health” aspect of the standard on individual manufacturers will result in most, and possibly all, such products being removed from the market.³⁵ It would also make it prohibitively difficult for any such new products to enter the market, which would be tantamount to a ban, despite Congress’s clear commitment to allow the marketing of potentially reduced risk products, as discussed below.

³⁴ *Id.*

³⁵ As discussed in Section IV below, based on the available scientific evidence, FDA should find that, generally, the availability of e-cigarettes on the market provides a public health benefit, as such products provide a much less harmful alternative to combustible cigarettes, and there is no reliable evidence that such products increase initiation of smoking. Such a finding would take the burden of demonstrating a positive population-level impact off of individual e-cigarette and e-liquid manufacturers. Manufacturers would still be required to demonstrate that their products do meet the “appropriate for the protection of the public health” standard, but by instead focusing on the impact of their product on the individual consumer, and not the potential *population level* impact.

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Another concern for FDA to consider is the potential that over-regulation by strictly applying the Tobacco Control Act requirements to these product could result in consumers turning to an unregulated “black market” if their products of choice are removed from the regulated market and/or effectively banned. A survey administered to 10,000 vapers by the E-Cigarette Forum found that 79% of respondents said they would “look to the black market” if products they use “were banned tomorrow,” while 14% said they would return to smoking analog cigarettes.³⁶ Such a result would be detrimental to the public health as such a black or grey market would be devoid of good product stewardship and manufacturing oversights/controls. The implications of such a market go beyond public health, as the economic and logistical burden (for enforcement efforts) is daunting.

v. The Primary Purpose Underlying the Tobacco Control Act is to Reduce Tobacco Related Disease and Death in the United States by Making it Nearly Impossible to Bring New, Harmful Tobacco Leaf-Containing Products to the Market

It is well established that tobacco leaf-containing products, and in particular, tobacco-*combusting* products, are detrimental to the health of individual consumers as well as to the public (*i.e.*, net population) health. According to the U.S. Centers for Disease Control and Prevention (CDC):³⁷

Tobacco use is the single most preventable cause of disease, disability, and death in the United States. Each year, an estimated 443,000 people die prematurely from smoking or exposure to secondhand smoke, and another 8.6 million live with a serious illness caused by smoking. Despite these risks, approximately 46.6 million U.S. adults smoke cigarettes. Smokeless tobacco, cigars, and pipes also have deadly consequences, including lung, larynx, esophageal, and oral cancers.

It is clear from its legislative history that, because of these well-known health consequences of tobacco use, the Tobacco Control Act was truly intended to apply to products that actually contain tobacco leaf, and to make it very difficult for the *tobacco industry* to bring

³⁶ See Nelson, S., *E-Cigarette Users Would Ignore Bans, Turn to Black Market, Survey Finds*, U.S. News & World Report, July 17, 2014, available online at: <http://www.usnews.com/news/articles/2014/07/17/e-cigarette-users-would-ignore-bans-turn-to-black-market-survey-finds>.

³⁷ See CDC, *Targeting the Nation's Leading Killer At A Glance 2011*, available online at: <http://www.cdc.gov/chronicdisease/resources/publications/aag/osh.htm>.

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such new products to the market. Specifically, before being able to bring a new product to the market, tobacco product companies have the heavy burden of demonstrating that such product is either substantially equivalent to a grandfathered product (*i.e.*, the new product is either identical to a grandfathered product or its different “characteristics” do not raise different questions of public health) or, in the alternative, that the new product is “appropriate for the protection of the public health” by way of a PMTA. Both the “different questions of public health” and “appropriate for the protection of the public health” standards for Substantial Equivalence (SE) Reports and PMTAs, respectively, are incredibly high and require considering the impact the new product will have on both users and non-users, as described above. In other words, both SE reports and PMTAs need to demonstrate that the introduction of the tobacco product in question will not result in increased harm to the public health by adversely impacting overall tobacco-use initiation and cessation rates.

It is illogical to place this same burden (which, again, was designed to make it nearly impossible to bring new harmful products to the market) on manufacturers of products that only contain tobacco-derived substances. Doing so will result in the vast majority of, if not all, such products being removed from the market. Congress, however, did not intend the implementation of the Tobacco Control Act to effectively ban products that have the potential to greatly reduce the burden on society of tobacco-related disease. When Congress passed the Tobacco Control Act it set out ten purposes underlying the legislation. These purposes include not only reducing “the social costs associated with tobacco-related diseases” and ensuring “that consumers are better informed”—but also continuing “to permit the sale of tobacco products to adults” and providing effective oversight of the “industry’s efforts to develop, introduce, and promote less harmful tobacco products.”³⁸ If the NPRM is implemented as drafted and the likely insurmountable burden of demonstrating the population level impact is placed on e-cigarette manufacturers, we do not believe the e-cigarette/e-liquid industry will survive. This would clearly go against Congress’ intent to reduce harm from tobacco-related disease through the promotion of less harmful products. The evidence suggests that Congress understood that the Tobacco Control Act was not intended to bring the tobacco industry to a grinding halt; rather, it sought only to establish “appropriate regulatory controls” over tobacco products.³⁹ FDA should take a similar approach in the Deeming Regulation to establish appropriate regulatory controls over e-cigarette and e-liquid products, as discussed in Section IV below.

³⁸ See 21 U.S.C. 387 et seq.

³⁹ *Id.* Congress, for example, gave FDA the authority to establish nicotine yields in Section 907 of the Act, but prohibited FDA from reducing the levels of nicotine in a product to zero, presumably because doing so would result in a de-facto ban on cigarettes, cigars, smokeless tobacco and roll-your-own tobacco products.

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vi. Proposed Legislation Governing the Marketing of E-cigarettes and E-liquids Makes Clear that Congress Does Not Intend for the Implementation of the Tobacco Control Act to Effectively Ban these Products for Adult Consumers

In *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 131-32 (2000), the U.S. Supreme Court was faced with a similar situation. In that case, the Supreme Court was charged with determining whether Congress had intended the FDCA to apply to conventional cigarettes and smokeless tobacco products. By way of background, although FDA historically maintained that it lacked jurisdiction under the FDCA to regulate “customarily marketed”⁴⁰ tobacco products, in 1996 the Agency proposed to regulate cigarettes and smokeless tobacco as drugs pursuant to its authority under the FDCA.⁴¹ Specifically, the FDA proposed to regulate the promotion, labeling, and accessibility of those customarily marketed tobacco products to children.

A group of tobacco manufacturers, retailers and advertisers filed a lawsuit against FDA, arguing that under the FDCA the Agency lacked jurisdiction to regulate tobacco products as customarily marketed and without express therapeutic or structure/function claims. FDA argued that customarily marketed cigarettes and smokeless tobacco products came under the Agency’s purview as drugs, because such products were nicotine delivery devices that, because of nicotine’s foreseeable addictive qualities and physiological effects on the body, were necessarily “intended” to affect the structure and function of the body.⁴² The Supreme Court

⁴⁰ Customarily marketed tobacco products are tobacco products marketed for recreational use or smoking pleasure, and not with any claims of therapeutic benefit or explicit structure/function claims.

⁴¹ The Supreme Court stated in that case:

In 1972, FDA Commissioner [Dr. Charles] Edwards testified before Congress that “cigarettes recommended for smoking pleasure are beyond the Federal Food, Drug, and Cosmetic Act.” He further stated that the FDA believed that the Public Health Cigarette Smoking Act “demonstrates that the regulation of cigarettes is to be the domain of Congress,” and that “labeling or banning cigarettes is a step that can be take[n] only by the Congress. Any such move by FDA would be inconsistent with the clear congressional intent.”

Id. at 151-52.

⁴² *Id.* at 131-32.

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disagreed with the Agency, however, and held that if FDA had jurisdiction over tobacco products through the FDCA, the Agency would have no choice but to remove and ban such products from the market entirely, as no tobacco leaf-containing product could meet the “safe and effective” standard for drugs, as tobacco leaf-containing products are inherently unsafe. But, the Supreme Court reasoned that banning tobacco products from the market would contradict Congress’s clear intent *not* to do so; such intent is demonstrated by, among other things, the fact that Congress has, over the years, enacted tobacco-specific legislation that does *not* ban such products.⁴³

Specifically, noting that it has directly addressed the problem of tobacco and health through legislation on numerous occasions, the Court stated that “Congress, however, has foreclosed the removal of tobacco products from the market.” The Court went on to state:⁴⁴

When Congress enacted these statutes, the adverse health consequences of tobacco use were well known, as were nicotine’s pharmacological effects. See, e.g., U.S. Dept. of Health, Education, and Welfare, U.S. Surgeon General’s Advisory Committee, Smoking and Health 25-40, 69-75 (1964) (hereinafter 1964 Surgeon General’s Report) (concluding that cigarette smoking causes lung cancer, coronary artery disease, and chronic bronchitis and emphysema, and that nicotine has various pharmacological effects, including stimulation, tranquilization, and appetite suppression); U.S. Dept. of Health and Human Services, Public Health Service, Health Consequences of Smoking for Women 7-12 (1980) (finding that mortality rates for lung cancer, chronic lung disease, and coronary heart disease are increased for both women and men smokers, and that smoking during pregnancy is associated with significant adverse health effects on the unborn fetus and newborn child); U.S. Dept. of Health and Human Services, Public Health Service, Why People Smoke Cigarettes (1983), in Smoking Prevention Education Act, Hearings on H. R. 1824 before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, 98th Cong., 1st Sess., 32-37 (1983) (hereinafter 1983 House Hearings) (stating that smoking is “the most widespread example of drug dependence in our country,” and that cigarettes “affect the chemistry of the brain and nervous system”); U.S. Dept. of Health and Human Services, Public Health Service, The Health Consequences of Smoking: Nicotine Addiction 6-9, 145-239 (1988) (hereinafter 1988 Surgeon General’s Report) (concluding that tobacco products are addicting in much the same way as heroin and cocaine, and that nicotine is the drug that causes

⁴³ *Id.* at 156.

⁴⁴ *Id.* at 138-139 (Emphasis added).

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addiction). **Nonetheless, Congress stopped well short of ordering a ban.** Instead, it has generally regulated the labeling and advertisement of tobacco products, expressly providing that it is the policy of Congress that “commerce and the national economy may be -- protected to the maximum extent consistent with” consumers “be[ing] adequately informed about any adverse health effects.” 15 U.S.C. § 1331. **Congress’ decisions to regulate labeling and advertising and to adopt the express policy of protecting “commerce and the national economy – to the maximum extent” reveal its intent that tobacco products remain on the market. Indeed, the collective premise of these statutes is that cigarettes and smokeless tobacco will continue to be sold in the United States. A ban of tobacco products by the FDA would therefore plainly contradict congressional policy.**

Accordingly, the Supreme Court in *Brown* ruled that at that time, Congress had not yet given FDA authority to regulate tobacco products as customarily marketed.⁴⁵

In this case, it is apparent that Congress similarly did not intend for the implementation of the Tobacco Control Act to effectively ban products such as e-cigarettes that do not contain tobacco leaf, as will likely happen if the burden of demonstrating the population level impact of a new product is placed on e-cigarette/e-liquid manufacturers. In addition to Congress’s clear statements regarding the purposes underlying the Act (*e.g.*, to reduce tobacco-related morbidity and mortality), there is much other evidence to indicate that it does not intend these products to be banned. More specifically, several standalone bills have recently been introduced that propose to restrict marketing of e-cigarettes, particularly any marketing directed toward children, but do not ban the products entirely or restrict their use by adults of legal smoking age.

For example, the Protecting Children from Electronic Cigarette Advertising Act of 2014 was recently introduced in both the Senate and House of Representatives.⁴⁶ This bill proposes to “prohibit advertisement, promotion, or marketing in commerce of electronic cigarettes in a manner that is known, or should be known, to increase the use of electronic cigarettes by children under the age of 18. Among other things, the bill also proposes to give the Federal Trade Commission (FTC) authority to enforce violations as an unfair or deceptive act or practice and to intervene and appeal in state actions. The bill does not ban or prohibit the use of e-cigarettes by adults.

⁴⁵ *Id.* at 176.

⁴⁶ *See* S. 2047 and H.R. 4325.

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Earlier this year, Congresswoman Jackie Speier announced plans to introduce the Stop Selling and Marketing to Our Kids E-Cigarettes (SMOKE) Act, which would similarly give the FTC authority “to prohibit the marketing, promotion, and advertising of electronic nicotine delivery systems or e-liquids that would increase usage of the products by children.” The proposed SMOKE Act would also amend the FCLAA so that electronic nicotine delivery systems and e-liquids can also be regulated like tobacco cigarettes, and, within one year of enactment, require FDA to establish (1) child-proof packaging standards for electronic nicotine delivery systems and e-liquids, (2) dosage limits for electronic nicotine delivery systems and e-liquids, (3) maximum levels of nicotine concentration and (4) labeling requirements to clearly state the concentration of nicotine for e-liquids. The proposed legislation also directs FDA to complete a study on whether flavorings help adults to quit smoking and/or appeal to children increasing their likelihood to use electronic nicotine delivery systems, and requires the Agency to consider prohibitions or restrictions on flavorings based on its findings.⁴⁷ Indeed, the purpose of the bill “is to make sure these products are safe, to keep consumers informed about important safety information such as dosage guidelines, and to keep these products out of the hands of teens and kids – especially the youngest children that run the highest risk of being poisoned.”

Even more recently, on July 10, 2014, Senator Bill Nelson introduced the Child Nicotine Poisoning Prevention Act of 2014, which would direct the Consumer Product Safety Commission to issue rules requiring safer, child-resistant packaging for any liquid nicotine sold to consumers.⁴⁸

Importantly, neither the Child Nicotine Poisoning Prevention Act, the Protecting Children from Electronic Cigarette Advertising Act, nor the SMOKE Act outlaw e-cigarettes for consenting adults. These proposed laws are designed to ensure that e-cigarettes and e-liquid products are safe and stay out of the hands of adolescents. Just as the FLCAA and CSTHEA made clear that Congress did not intend to effectively ban traditional cigarette and smokeless tobacco by giving FDA authority over such products under the drug provisions of the FDCA, the proposed legislation governing the marketing of e-cigarettes makes clear that Congress does not

⁴⁷ See Congresswomen Speier Introduces SMOKE Act to Regulate E-cigarette Products, available online at: http://www.jackiespeier.house.gov/index.php?option=com_content&view=article&id=1460:congresswomen-speier-introduces-smoke-act-to-regulate-e-cigarette-products&catid=20:press-releases&Itemid=14.

⁴⁸ See Child Nicotine Poisoning Prevention Act of 2014, available online at: <https://www.govtrack.us/congress/bills/113/s2581>.

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intend for the implementation of the Tobacco Control Act to effectively ban e-cigarettes and e-liquids for adult consumers.

In addition to these proposed bills, earlier this year several U.S. Congressmen and Senators sent a letter to the Attorney Generals in California, Iowa and Vermont requesting they “consider taking a bold step in the battle against tobacco use” by classifying e-cigarettes as *cigarettes* under the Master Settlement Agreement (MSA).⁴⁹ Notwithstanding that e-cigarettes simply do not fall within meaning of cigarettes in the MSA⁵⁰, the U.S. lawmakers also state in the letter that “[b]ringing e-cigarettes under the [MSA] would not remove them from the market or make them unavailable to adults who may see them as safer alternative to conventional cigarettes,” clearly indicating their intent that the products not be banned.

Strictly applying the Tobacco Control Act requirements to these novel products would be tantamount to a ban, and would defy Congressional intent.

⁴⁹ See Letter from Senators Waxman, Harkin and Welch to Attorneys General Harris, Miller and Sorrell, available online at: <http://democrats.energycommerce.house.gov/sites/default/files/documents/Harris-Miller-Sorrell-Master-Settlement-Agreement-Tobacco-2014-2-12.pdf>.

⁵⁰ The MSA defines cigarettes as “any product that contains nicotine, is intended to be burned or heated under ordinary conditions of use, and consists of or contains (1) any roll of tobacco wrapped in paper or in any substance containing tobacco; or (2) tobacco, in any form, that is functional in the product, which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette; or (3) any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette described in clause (1) of this definition. See MSA (1998) online at <http://oag.ca.gov/sites/all/files/agweb/pdfs/tobacco/1msa.pdf>. As noted above, neither e-cigarettes nor the e-liquid used in them contain any tobacco at all. Although it may be *derived* from tobacco, nicotine is a chemical compound identified in Section 900(12) of the Tobacco Control Act as “3-(1-methyl-2-pyrrolidinyl) pyridine or C[10]H[14]N[2], including any salt or complex of nicotine” and is not itself “tobacco.” Accordingly, e-cigarettes and e-liquid that contain tobacco-derived nicotine do not meet any of the criteria for being a “cigarette” in the MSA.

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vii. If Congress Intended the Tobacco Control Act to Result in an Effective Ban on E-Cigarettes, it Would Not Have Defined “Tobacco Product” so Broadly to Include Products that Only Contain Tobacco-Derived Substances

Furthermore, Congress clearly did not intend for the Tobacco Control Act to effectively ban novel nicotine-only products like e-cigarettes, as it already had the capability to do this by way of its drug authority under the FDCA. Prior to the implementation of the Tobacco Control Act, nicotine-containing products such as e-cigarettes would have been considered drugs (or drug-delivery devices).⁵¹ This was the position that FDA took prior to the implementation of the Tobacco Control Act for other “nicotine delivery” products such as the FAVOR® Smokeless Cigarette,⁵² Nicogel Tobacco Hand Gel, nicotine lollipops, nicotine lip balm and nicotine water.

⁵¹ Section 321(g)(1) of the FDCA defines “drug,” in pertinent part, as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” See 21 U.S.C. § 321(g)(1)(B) and (C).

⁵² In the 1980s, the FAVOR® Smokeless Cigarette was marketed as a “revolutionary new cigarette” that gave “customers tobacco flavor and satisfaction with no smoke.” The FAVOR® consisted of a tube of cellulose acetate wrapped with cigarette paper and topped with brown cork tipping. The tube was filled with liquid nicotine blended with flavor enhancers used in traditional cigarettes. When air is drawn through the tube, the liquid turned into a colorless, odorless vapor with a cigarette-like taste. Although the manufacturer of that product did not promote the FAVOR® as a smoking cessation tool, but as a recreational, non-therapeutic nicotine product that could provide a less harmful way for smokers to continue “smoking,” FDA asserted that the product was an unapproved new drug that could not be sold without FDA pre-market approval. In a Warning Letter to the manufacturer dated February 9, 1987, FDA stated:

The [Favor product’s labeling and promotional literature] contain statements which represent and suggest that Favor is a novel nicotine delivery system; that each pack of six [Favor tubes] will have a nicotine delivery capacity intended to satisfy the average smoker of conventional cigarettes for an entire day; that Favor delivers an amount of nicotine per inhalation within a range of amounts delivered per inhalation from many conventional combustible cigarettes; that the quantity of nicotine required to produce the effect on the nervous system which most cigarette smokers are accustomed is small relative to the amounts of other alkaloids regularly consumed by typical users; and that it is an alternative for conventional cigarette smokers who desire nicotine pleasure.

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It is also the position that FDA initially took with respect to e-cigarettes, before the *Sottera* decision.⁵³

As the *Sottera* case made clear, however, the implementation of the Tobacco Control Act created a new paradigm that permits the marketing of recreational use nicotine-containing products as tobacco products and not drugs.⁵⁴ In this regard, the enactment of the Tobacco Control Act actually *prevented* the immediate ban of these products, which otherwise would have *only* been allowed to market if they received FDA premarket approval by demonstrating safety and effectiveness for a therapeutic purpose (*e.g.*, smoking cessation or to satisfy nicotine cravings), regardless of whether such products were customarily marketed for recreational use. But, by defining “tobacco product” broadly in the Tobacco Control Act to include products that

(...continued)

* * *

In view of the above, it is our position that Favor is a nicotine delivery system intended to satisfy nicotine dependence and to affect the structure and one or more functions of the body. Because of its intended uses, Favor is a drug as defined within section 201(g) of the Federal Food, Drug and Cosmetic Act (Act). In addition, we regard Favor to be a new drug within the meaning of section 201(p) of the Act because Favor’s composition is such that it is not generally recognized, among qualified experts, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling.

⁵³ See *Sottera, Inc. v. FDA*, 627 F.3d 891 (D.C., 2010)).

⁵⁴ Specifically, the D.C. Court of Appeals in *Sottera* affirmed the District Court’s decision which held, in pertinent part, that if it e-cigarettes were considered drugs simply because they have the same effect on the structure and function of the body as cigarettes, “any tobacco product containing nicotine and claiming to have some pharmacological effect, including traditional cigarettes, would be excluded from the meaning of ‘tobacco product.’” See *Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 70 (D.D.C., 2010). Because this would “effectively dismantle the existing regulatory wall Congress erected between tobacco products and drug-device combinations,” the court could “easily infer that Congress did not intend tobacco products to be drugs merely because they deliver nicotine.” *Id.* Thus, e-cigarettes that contain nicotine-derived tobacco that are customarily marketed for recreational use are not drugs if they simply deliver nicotine and affect the structure and function of the body in the same manner as a cigarette.

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only contain tobacco-derived substances while *not* giving FDA immediate authority to regulate all such tobacco products, Congress created the regulatory environment that allowed for these customarily marketed nicotine-only products to flourish on the market. Essentially, if not for the Tobacco Control Act, the e-cigarette industry would not even exist in the U.S. today.

It simply does not make sense to assert that Congress intended FDA to strictly apply the Tobacco Control Act requirements to novel nicotine-only products if doing so would result in such products being removed from the market and effectively banned, as FDA already had the authority to do just that through the drug provisions of the FDCA. If Congress truly intended the Tobacco Control Act to have such an impact on nicotine-only products, it would have either not defined “tobacco product” to include tobacco-derived substances, or it would simply have given FDA the immediate authority to regulate all tobacco products, including nicotine-only products, under its new found tobacco authority, rather than allowing FDA to choose which other tobacco products to deem as regulated products.

We further note that Section 907(d)(3) of the Tobacco Control Act makes clear that Congress did not intend for the new law to ban whole categories of tobacco products. Although that provision states that FDA cannot issue a *regulation* “banning all cigarettes, all smokeless tobacco, all little cigars, all cigars other than little cigars, all pipe tobacco, or all roll-your-own tobacco products,” this language implies that Congress did not intend for FDA to implement the law in such a way that would result in a tantamount ban of any tobacco product categories, much less a deemed product category that is demonstrably less harmful than the currently regulated tobacco leaf-containing products (*e.g.*, e-cigarettes), and that could provide a substantial public health benefit to current smokers.

For the reasons stated above, there is no doubt that Congress did not intend for e-cigarettes to be effectively banned by the Tobacco Control Act, which is what will occur if the premarket authorization requirements designed to make bringing new *tobacco leaf-containing* products to the market as difficult as possible are applied to these novel *tobacco leaf-free* products. It is clear that FDA has the discretion to impose on those other tobacco products that it chooses to regulate requirements that are tailored to the specific tobacco type and commensurate with the harm that requires regulation. In Section IV below, we propose several alternative regulatory frameworks for e-cigarette and e-liquid products for FDA to consider. Namely, we think that:

1. Based on the extensive existing literature on the safety and public health benefit of e-cigarettes (compared to conventional cigarettes) the Agency should acknowledge that a less rigorous implementation of premarket documentation is appropriate. Specifically, FDA should find that, as a class of products, the availability of e-cigarettes and their e-liquid components are “appropriate for the protection of the public health”. Accordingly, e-cigarette and e-liquid manufacturers should not have to consider the potential

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population-level impact of their products, but should instead only be required to demonstrate that their products are not unnecessarily harmful to the health of individual consumers by, for example, complying with product standards and Good Manufacturing Practices. FDA should delay the effective date of the Deeming Regulation until it is ready to promulgate industry-specific product standards and GMPs for these products.

2. If FDA chooses to deem e-cigarettes as regulated tobacco products, only the cigarette-look-alike or “cigalike” models and not advanced refillable personal vaporizers (ARPVs) should be considered “covered tobacco products” under the Deeming Regulation, for the same reasons that FDA has suggested exempting premium cigars from regulation under Option 2 of the NPRM. Moreover, the component parts of such products should not be considered covered tobacco products.
3. FDA should use the effective date of the final rule for the Deeming Regulation as the new “Grandfather Date” for e-cigarettes and e-liquid products and model the substantial equivalence requirements for these products based on the Section 510(k) pathway for medical devices.
4. FDA should implement an alternative framework for e-liquid manufacturing companies to comply with Section 904(a)(1) ingredient listing requirement and establish a “master file” system for industry suppliers and component manufacturers to submit confidential information.

We review each of these regulatory frameworks, in turn, below.

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IV. Potential Regulatory Frameworks for Electronic Cigarettes and Components

- a. Regulatory Framework No. 1: FDA Should Only Require E-Cigarette and E-liquid Manufacturing Companies to Consider the Impact of their Products on the Health of the Individual Consumer, and not the Population Level Impact, To Meet the “Appropriate for the Protection of the Public Health” Legal Standard**
 - i. FDA Should Find That, As A Class of Products, The Availability of E-Cigarettes and Personal Vaporizers is Appropriate for the Protection of the Public Health**

Based on the growing body of data which establishes that e-cigarettes and the e-liquids used in them (1) provide a much less harmful alternative to tobacco leaf-containing products (especially combustible cigarettes) for current tobacco users and (2) do not have an adverse impact on smoking initiation and cessation rates (*i.e.*, the evidence indicates that the products have contributed to the continuing decline in the percentage of the population that smokes cigarettes), FDA should find that, generally, the availability of these products on the market is “appropriate for the protection of the public health”. It is critically important for FDA to acknowledge that it is not starting from a *tabula rasa* when it comes to understanding the safety of nicotine aerosols for inhalation using electronic cigarettes. Instead of pretending that we know nothing about the safety of the inhalation of nicotine and propylene glycol (as well as other commonly used diluents like glycerin), FDA should acknowledge that, as a class of devices (*i.e.*, a device producing a nicotine aerosol for inhalation produced through electric heating of a liquid mixture of nicotine and propylene glycol/glycerin diluent) e-cigarettes meet the public health requirement of the Tobacco Control Act. In other words, FDA should adopt an alternative regulatory framework for these novel products whereby individual e-cigarette and e-liquid manufacturing companies need not affirmatively demonstrate that each of their products will have a positive net-population level “public health” impact. Rather, in order to meet the “appropriate for the protection of the public health” legal standard, such companies need only consider the impact of their product on the health of individual consumers by demonstrating that their products are compliant with established product standards, manufactured in accordance with Good Manufacturing Practices and marketed responsibly toward adult consumers.

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1. To Meet the Appropriate for the Protection of the Public Health Standard FDA Should Only Require E-Cigarette and E-liquid Manufacturing Companies to Consider the Impact of their Products on the Health of the Individual Consumer and not the Population Level Impact

In order to demonstrate that a new tobacco product is “appropriate for the protection of the public health” the Tobacco Control Act requires tobacco product manufacturers to consider both users and non-users and show that the availability of the new product will not adversely impact overall smoking initiation and cessation rates. However, without long-term consumer perception and post-market data, among other things, this standard is insurmountable for most, and possibly all, e-cigarette and e-liquid manufacturing companies, and would result in potentially all such products being removed/banned from the market, notwithstanding Congress’ clear intent described above. Instead of placing the burden on individual e-cigarette and e-liquid manufacturers to affirmatively demonstrate that their products will not adversely impact overall smoking initiation and cessation rates by way of a premarket tobacco product application (PMTA), FDA should, considering the available scientific evidence, find that the availability of e-cigarettes is, generally, appropriate for the protection of the public health because (a) the products provide a much less harmful alternative to combustible cigarettes and (b) the evidence indicates that the products have contributed to the continuing decline in the percentage of the population that smokes cigarettes.⁵⁵ Such a general finding by FDA would in and of itself be appropriate for the protection of the public health, as it would allow these reduced harm products to remain on the market as an alternative for smokers of combustible cigarettes, and would make it much less difficult for manufacturers to bring new products to the market.

Of course, manufacturers would still be required to demonstrate that their products do meet the “appropriate for the protection of the public health” standard, but by instead focusing on the impact of their product on the health of the *individual* consumer, and not the potential population-level impact. This means that in order to forgo the population-level assessment, e-cigarette and e-liquid manufacturers need only consider the impact of their product on the health of individual consumers by, for example, demonstrating that their products are compliant with established product standards, manufactured in accordance with Good Manufacturing Practices and marketed responsibly toward adult consumers.

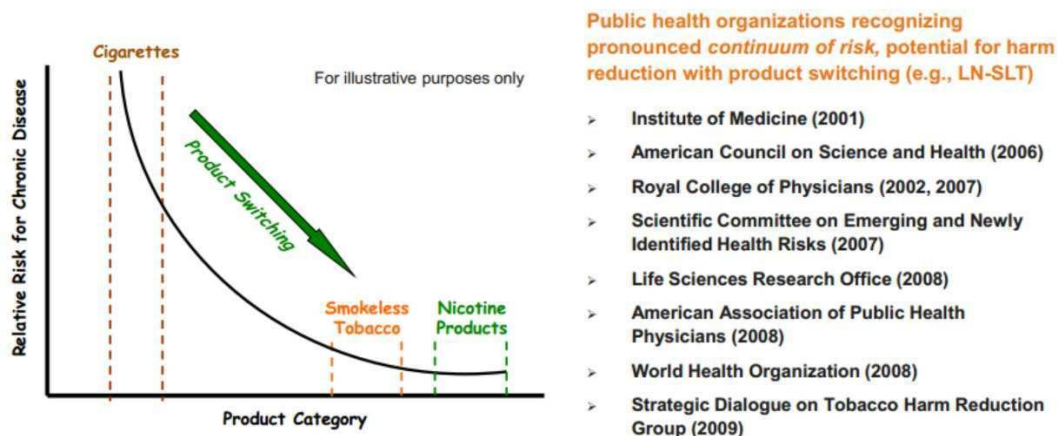
⁵⁵ This is indicated by the declining smoking rate as reported by the CDC as well as the correlative reduction in recent tobacco cigarette sales and the comparable, and simultaneous, dramatic e-cigarette/vapor market explosion clearly indicating that smokers are substituting their cigarettes for these products.

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To support a finding that the general availability of e-cigarettes and e-liquids on the market is appropriate for the protection of the public health, we examine below the growing body of data which establishes that e-cigarettes and the e-liquids used in them (1) provide a much less harmful alternative to tobacco leaf-containing products (especially combustible cigarettes) for current tobacco users and (2) do not have an adverse impact on smoking initiation and cessation rates (*i.e.*, these products are *not* causing the overall smoking rate to increase).

a. Electronic Cigarettes Provide a Much Less Harmful Alternative to Tobacco Leaf-Containing Products for Current Tobacco Users, Especially Smokers

There is no doubt that compared to tobacco-leaf products, and especially those that are combusted, e-cigarettes and the e-liquids used in them are dramatically less harmful for individual tobacco users, especially cigarette smokers. This is why when tailoring the regulatory requirements for the tobacco products FDA chooses to deem as regulated, the Agency should recognize the wide disparity of risk posed by different types of products. This risk disparity can be described on a “continuum of risk,” whereby the products that pose the greatest harm and risk of tobacco-related disease (*i.e.*, the traditional, combustible cigarette) is on one end of the continuum, and new product forms (such as e-cigarettes) that do not contain or combust tobacco leaf are on the other end, as depicted in the following diagram⁵⁶:



Tobacco leaf-containing products, especially those that are combusted, are the most harmful and dangerous products on the continuum of risk and should be treated as such. It is

⁵⁶ FDLI, Embracing the Continuum of Risk, (2013), available online at: <http://www.fdpi.org/docs/default-document-library/6---tobacco---combined.pdf?sfvrsn=0>.

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well established that the more pyrolyzed tobacco constituents a user inhales from a combustible tobacco product, such as a cigarette, the greater the risk of tobacco-related disease that product poses.⁵⁷ Of the approximately 5,300 chemicals identified in tobacco smoke, at least 60 are known human carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs).⁵⁸ Electronic cigarettes are far less risky to individual users than combustible cigarettes because they do not result in the inhalation of pyrolyzed chemicals.

Public health experts around the world have come out in support of tobacco harm reduction through the use of e-cigarettes. More than 50 tobacco and nicotine and public health specialists from 15 countries recently sent a letter to the World Health Organization (WHO) Director General Margaret Chan emphasizing the importance of tobacco harm reduction through the use of “low risk non-combustible tobacco products (which includes e-cigarettes). These products “could be among the most significant health innovations of the 21st Century—perhaps saving hundreds of millions of lives.”⁵⁹ Similarly, with respect to the impact on the individual consumer, the American Legacy Foundation, a not-for-profit organization dedicated to preventing teen smoking and encouraging smokers to quit, recently published a position statement on e-cigarettes, in which it stated: “Legacy recognizes that, on an individual level, there is a continuum of risk across tobacco products with combustible products (*e.g.*, cigarettes, cigars, hookah) posing the most danger and Food and Drug Administration (FDA) approved nicotine replacement therapies (NRT’s) posing the least harm. Harm reduction is a valuable public health strategy with the potential to reduce, although not eliminate, the preventable disease and death caused by tobacco. Electronic cigarettes may hold great promise in this regard. While they are not without risk, initial scientific evidence suggests that, for the individual smoker, they are likely less harmful than smoking cigarettes, and they likely have significant lower levels of known tobacco toxicants than combusted tobacco products.”⁶⁰

⁵⁷ See R.R. Baker, *et al.*, *The pyrolysis of tobacco ingredients*, 71 J. Anal. Appl. Pyrolysis 223-311 (2004).

⁵⁸ See Rodgman, A. and Perfetti, T.A., *The Chemical Components of Tobacco and Tobacco Smoke*, Boca Raton, FL: CRC Press (2009).

⁵⁹ See David Abrams *et al.*, *Statement from specialists in nicotine science and public health policy*, (2014), <http://www.nicotinepolicy.net/documents/letters/MargaretChan.pdf>.

⁶⁰ See Legacy, *E-cigarette policy: the FDA should promptly exercise regulatory authority over e-cigarettes*, (2014), http://www.legacyforhealth.org/content/download/3962/56088/version/1/file/LEG-Policy_Statement-ECigarette-JAN2014.pdf.

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The potential for e-cigarettes to be used as a valuable tool for harm reduction must be considered, especially in light of the effectiveness (or lack thereof) of FDA-approved NRT products. The Alpert et al. study casts serious doubt on the efficacy of FDA-approved NRT treatments, such as patches, gum, and drugs, such as Zyban and Chantix.⁶¹ As Michael Marlow noted in his public comment on behalf of the Mercatus Center at the George Mason University: “This study concludes that persons who have quit smoking relapsed at equivalent rates, whether or not they used NRT to help them in their quit attempts. In other words, FDA-approved NRT may not be any more effective in helping smokers quit their smoking habits than going ‘cold turkey.’ The possibility that e-cigarettes represent a market response that attempts to fill the need for harm reduction by smokers is worth pursuing. This is especially true given concerns over the efficacy of NRT.”⁶²

We review the impact of e-cigarettes and e-liquids, generally, on the health of individual consumers compared to tobacco-leaf products below.

**i. Compared to Cigalike Electronic Cigarettes,
Advanced Refillable Personal Vaporizers are
Less Harmful to the Health of Individual
Consumers**

Electronic cigarettes are a new and rapidly evolving technology. In order to effectively regulate these products, it is critical for FDA to understand the distinctions within the category. All e-cigarettes operate in the same basic way – they are battery-powered devices that provide inhaled doses of aerosolized nicotine. When a user inhales/puffs on the device, the heating element known as the atomizer (or cartomizer, in some cases⁶³) vaporizes the e-liquid solution contained in the cartridge/tank into an aerosol. When the user inhales on the device, this action “pulls” the liquid from the atomizer’s reservoir into the atomizer pot. This liquid is then absorbed by the aromatic polyimide wick (which is situated inside the pot). At the same time, the device is heating the coil around the wick and therefore heating the e-liquid until it becomes an aerosol.

⁶¹ Hillel R. Alpert, et. al, *A Prospective Cohort Study Challenging the Effectiveness of Population-based Medical Intervention for Smoking Cessation*, Tobacco Control 22 (2013): 32-37.

⁶² Marlow ML, available online at:
http://mercatus.org/sites/default/files/Marlow_ecig_PIC_062714.pdf.

⁶³ The atomizer is the part that turns the liquid into vapor. It does this by heating a coil that is in contact with the filler material containing the e-liquid. Cartomizers are a combination cartridge and atomizer.

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This aerosol contains the nicotine and other components such as propylene glycol/vegetable glycerin (PG/VG) and flavor compounds inhaled by the consumer when it is drawn up through the e-cigarette and out of the mouthpiece. But as we have indicated, there are two distinct types of e-cigarettes: cigarette-look-alike or “cigalike” devices and advance refillable personal vaporizers (ARPVs).

Cigalikes were the first type of e-cigarette to enter the market and are designed to mimic the look and feel of a traditional, combustible cigarette. These devices are closed-system products, meaning the nicotine-containing e-liquid solution comes in prefilled replaceable cartridges/cartomizers. Most cigalike e-cigarettes are rudimentary devices that were not designed with consumer safety in mind. As a result, over the last few years we have seen a growing number of more advanced e-cigarettes enter the market. Compared to the early cigalike models, these ARPVs are better designed, incorporate numerous safety features and provide more consistent and effective aerosol/nicotine delivery. These products utilize new-generation high-capacity batteries with electronic circuits that provide high energy to a refillable atomizer. For a summary of e-cigarette and ARPV components, see: <http://www.mister-e-liquid.com/electronic-cigarette-terminology>. Examples of typical ARPV safety features include:

- Microprocessors used to monitor and adjust the power and heat delivered, ensuring consistent aerosol delivery;
- Over/under-charge and short-circuit protections (internal on device circuit boards);
- “Smart charging” ability using cell phone technology which stops charging current flow to battery when fully charged;
- Newer refillable tanks/atomizers do not contain the cartomizer filler material found in cigalikes, which has the potential to melt/char if heated after the e-liquid is consumed;
- “Boost circuits” which help to ensure consistent aerosol output by maintaining the heat level, as well as offer adjustable airflow features allowing the user to customize their experience and prevent potential “dry puff”; and
- Safety feature in the power on/off mechanism which requires users to press the power button several times in succession to power the device. This prevents unintentional activation.

The innovative ARPV industry is continually incorporating more advanced technology to improve the quality and safety of their products. We discuss the *public* (population level) health benefits of ARPVs compared to cigalikes below in Section IV(a)(i)(1)(a)(iii).

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ii. Safety of Nicotine

Nicotine, of course, is the component of most concern in e-liquids. It is well established, however, that while nicotine is not, *per se*, harmless, it is *not* the substance that kills smokers. As Mitch Zeller, the Director of FDA's Center for Tobacco Products has stated on several occasions, people may smoke cigarettes for the nicotine, but die from inhaling the smoke and tar from combusting tobacco. The safety and toxicological profile of nicotine has been studied extensively in both animals and man, and a comprehensive survey of this literature will not be presented here. We do note that, importantly, nicotine itself is not a carcinogen. The long-term inhalation effects of nicotine have been studied over a two-year period in 68 female Sprague-Dawley rats (34 control animals).⁶⁴ After being exposed to pure nicotine aerosol for 20 hours a day for five days a week for over two years, no tumorigenic effects of nicotine were found in any organ in the body. No tumors were detected on either microscopic or macroscopic examination of the lungs. There were also no changes evident in the macroscopic examination of the hearts, including atherosclerotic lesions (although some nicotine-exposed animals did develop pituitary tumors).

Studies on the long-term use of nicotine-replacement therapies (NRTs) have similarly made clear that nicotine is also not a carcinogen in humans. Specifically, a connection between nicotine and cancer was not found in a 5-year study of 5,887 subjects. In that study, the researchers concluded that "[t]he absence in general of a relation between nicotine replacement therapy and cancer across the models adds credence to our conclusion that nicotine replacement therapy does not cause cancer." FDA itself has confirmed this in its Notice of Findings published last year for "Modifications To Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use".⁶⁵ In that notice, FDA cites a growing body of evidence that demonstrates the safety of long-term nicotine use as well as that NRT products sold over-the-counter (OTC) do not appear to have significant potential for abuse or dependence. Considering this, FDA requested NRT manufacturers to submit supplemental new drug applications to change the labeling of their current NRT products to make clear that, among other things, that it is safe for users of NRT products to use such products beyond the 8-12 weeks on the label in order to quit smoking.

Of course, we recognize that nicotine does pose some acute hazards if swallowed or absorbed through the skin and, as a result of the increasing market share of ARPVs, the growing

⁶⁴ See Waldhum, H.L. et al., *Long-term effects of inhaled nicotine*, 58(16) Life Sciences 1339-1346 (1996).

⁶⁵ See 78 Fed. Reg. 19718 (April 2, 2013).

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presence of refillable e-liquids on the marketplace, and in the home, expands the population that may be inadvertently exposed to nicotine at levels that pose an acute toxicity risk. But first, it is important to recognize that, contrary to popular belief, the lethal dose of nicotine for adults (when ingested) is between 500-1000 mg (not 50-60 mg as many still believe).⁶⁶ Nevertheless, risks associated with these hazards can be controlled by careful attention to how these products are packaged. AEMSA fully supports the safe handling of nicotine-containing e-liquids by adults through the use of child-proof packaging and other means.

It is also critical to understand the context of the potential harm. Recent media reports about the rising dangers of nicotine exposures from e-liquids greatly exaggerate the level of harm. According to the National Poison Data System (NPDS), e-cigarettes account for only 0.1% of exposures reported to Poison Control Centers (*i.e.*, 200 of 194,500 monthly calls).⁶⁷ Other common household goods result in far more reported poisoning cases. According to NPDS's annual report from 2012, the top five substance classes most frequently involved in all human exposures were analgesics (11.6%), cosmetics/personal care products (7.9%), household cleaning substances (7.2%), sedatives/hypnotics/antipsychotics (6.1%), and foreign bodies/toys/miscellaneous (4.1%). Analgesic exposures as a class increased the most rapidly (8,780 calls/year) over the last 12 years. The top five most common exposures in children aged 5 years or less were cosmetics/personal care products (13.9%), analgesics (9.9%), household

⁶⁶ See Farsalinos, KE, *Nicotine lethal dose in humans: a common argument by regulatory authorities, based on poor science*, available online at: <http://ecigarette-research.com/web/index.php/2013-04-07-09-50-07/132-nicotine-lethal-dose-in-humans>.

⁶⁷ In 2012, there were 2,275,141 exposures reported to Poison Control Centers, or 189,595 exposures per month. See James Mowrey *et al.*, *2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report*, (2013), https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2012_NPDS_Annual_Report.pdf. Considering this in light of the CDC's recent announcement that e-cigarette calls to Poison Control Centers have increased to about 200 per month, it is clear that e-cigarettes account for only a tiny fraction (0.1%) of reported exposures (*i.e.*, 200 of 189,595 monthly calls). See CDC, *Notes from the Field: Calls to Poison Centers for Exposures to Electronic Cigarettes — United States, September 2010–February 2014*, (2014), http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6313a4.htm?s_cid=mm6313a4_e.

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cleaning substances (9.7%), foreign bodies/toys/ miscellaneous (7.0%), and topical preparations (6.3%).⁶⁸

iii. Studies Demonstrating the Safety of E-Cigarettes and E-Liquids Compared to Tobacco Leaf Products

There are dozens of studies in the public literature (and growing) that scientifically demonstrate that e-cigarettes and the e-liquid used in them are demonstrably less harmful for individual consumers compared to tobacco leaf-containing products. We highlight some of these studies below:

- A team of researchers led by Dr. Thomas Eissenberg, co-director of the Center for the Study of Tobacco Products at Virginia Commonwealth University, reviewed 81 prior studies of the pharmacodynamics, pharmacokinetics, and health impact of e-cigarettes including chemicals in the liquids and aerosols and use among smokers and non-smokers.⁶⁹ The purpose of the study, which was partly funded by the U.S. National Institutes of Health and published in the journal *Addiction* on July 30, 2014, was to assess the potential for harm or benefit of e-cigarettes and to obtain evidence to guide future policy. The researchers determined that while e-cigarette aerosol can contain some of the toxicants present in tobacco smoke, the levels are much lower. Moreover, while long-term health effects of e-cigarette use are unknown, compared with combustible tobacco cigarettes, e-cigarettes are likely to be much less, if at all, harmful to users or bystanders. The study authors concluded that allowing e-cigarettes to compete with tobacco cigarettes in the market place might decrease smoking-related morbidity and mortality. Regulating these as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted based on the current evidence.

⁶⁸ See Mowry, *et. al.*, 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report., 51(10), Clin. Toxicol. 949-1229 (2013). ; See CDC, 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report.

⁶⁹ See Hajek, P., Etter, J.-F., Benowitz, N., Eissenberg, T. and McRobbie, H. (2014), *Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit*, *Addiction*, doi: 10.1111/add.12659, available online at: <http://onlinelibrary.wiley.com/doi/10.1111/add.12659/full>.

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- Similarly, Drs. Konstantinos Farsalinos and Riccardo Polosa of the Centro per la Prevenzione e Cura del Tabagismo (CPCT) and Institute of Internal Medicine, Università di Catania, Catania, Italy, conducted a systematic review of existing laboratory and clinical research on the potential risks from e-cigarette use, compared with the well-established devastating effects of smoking tobacco cigarettes.⁷⁰ The researchers concluded that currently available evidence indicates that e-cigarettes are by far a less harmful alternative to smoking cigarettes, and significant health benefits are expected in smokers who switch from tobacco to e-cigarettes. Research will help make e-cigarettes more effective as smoking substitutes and will better define and further reduce residual risks from use to as low as possible, by establishing appropriate quality control and standards.
- An international expert panel convened by the Independent Scientific Committee on Drugs recently demonstrated that use of e-cigarettes is far less risky compared to the use of traditional combustible tobacco, and only slightly more risky than FDA-approved nicotine replacement products that are recognized as being safe for their intended use.⁷¹ More specifically, the expert panel developed a multi-criteria decision analysis model of the relative importance of different types of harm related to the use of nicotine-containing products (e.g., cigarettes, cigars, water pipes, smokeless tobacco, electronic nicotine delivery systems, nicotine patch and nasal spray). After defining the products and the harm criteria the group scored all the products based on each criterion to determine the product's average harm worldwide. The products were compared to each other using a scale with 100 defined as the most harmful product on a given criterion, and a score of zero defined as no harm. The panel found that the weighted averages of the scores provided a single, overall score for each product. Cigarettes (overall weighted score of 100) emerged as the most harmful product, with small cigars in second place (overall weighted score of 64). After a substantial gap to the third-place product, pipes (scoring 21), all remaining products, including e-cigarettes, scored 15 points or less. The panel concluded that cigarettes cause by far the most harm and attempts to encourage smokers to switch to non-combusted sources of nicotine should be encouraged.

⁷⁰ See Farsalinos KE and R. Polosa, *Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review*, 5 Therapeutic Advances in Drug Safety 67-86 (2014), abstract available online at: <http://taw.sagepub.com/content/early/2014/02/12/2042098614524430.abstract>.

⁷¹ See Nutt, D.J. et. al, *Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach*, 20 European Addiction Research 218 (2014), abstract <http://www.karger.com/article/fulltext/360220>.

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- According to a new study published in the International Journal of Environmental Research and Public Health, asthmatic smokers who use e-cigarettes experience an improvement in their asthma symptoms and lung function, even if they remain dual users.⁷² The study examined 18 smokers with significant asthma who switched to electronic cigarettes. Ten of the patients switched completely and 8 became dual users (both smoking and using e-cigarettes). Among the dual users, the average cigarette consumption dropped from 22.4 to 3.9 cigarettes per day. After one year follow-up, both the ex-smokers and dual users experienced a significant improvement in asthma symptoms and lung function, especially small airways obstruction. Although the improvements in lung function were small, the improvements in asthma symptoms were clinically relevant. The study authors concluded that by substantially reducing the number of cigarettes smoked per day and exposure to their hazardous toxicants, e-cigarettes may not only improve asthma symptoms and pulmonary function but may also confer an overall health advantage in smokers with asthma.
- With respect to the cardiovascular effects of e-cigarette use, a study was recently performed to examine the immediate effects of e-cigarette use on left ventricular (LV) function, compared to the well-documented acute adverse effects of smoking.⁷³ Specifically, echocardiographic examinations were performed in 36 healthy adult heavy smokers before and after smoking one cigarette, and in 40 electronic cigarette users before and after using the device with “medium-strength” nicotine concentration (11 mg/mL) for 7 minutes. Mitral flow diastolic velocities (E, A), their ratio (E/A), deceleration time (DT), isovolumetric relaxation time (IVRT) and corrected-to-heart rate IVRT (IVRTc) were measured. Mitral annulus systolic (Sm), and diastolic (Em, Am) velocities were estimated. Myocardial performance index was calculated from Doppler flow (MPI) and tissue Doppler (MPIt). Longitudinal deformation measurements of global strain (GS), systolic (SRs) and diastolic (SRe, SRa) strain rate were also performed. Baseline measurements were similar in both groups. In SM, IVRT and IVRTc were prolonged, Em and SRe were decreased, and both MPI and MPIt were elevated after smoking. In ECIG, no differences were observed after device use. Comparing after-use

⁷² See Polosa R, *et al.* *Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal*, 11(5) Int. J. Environ. Res. Public Health 4965-4977 (2014), available online at: <http://www.mdpi.com/1660-4601/11/5/4965>.

⁷³ See K. Farsalinos, *et al.*, *Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes*, 14 BMC Cardiovascular Disorders 78 (2014) available online at: <http://www.biomedcentral.com/1471-2261/14/78>.

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measurements, ECIG had higher Em ($P = 0.032$) and SRe ($P = 0.022$), and lower IVRTc ($P = 0.011$), MPI ($P = 0.001$) and MPIt ($P = 0.019$). The observed differences were significant even after adjusting for changes in heart rate and blood pressure. The study authors concluded that although acute smoking causes a delay in myocardial relaxation, e-cigarette use has no immediate effects.

- Independent university researchers analyzed data from a pilot online survey to determine whether switching to e-cigarettes from combustible cigarettes had any influence on the health of the consumer. All respondents previously smoked and 91% had attempted to stop smoking before trying e-cigarettes. Most respondents resided in the United States (72%) and 21% were in Europe. About half (55%) were 31-50 years old, while 32% were >50 years old. Most (79%) of the respondents had been using e-cigarettes for less than 6 months and reported using them as a complete (79%) or partial (17%) replacement for, rather than in addition to (4%), cigarettes. The majority of respondents reported that their general health (91%), smoker's cough (97%), ability to exercise (84%), and sense of smell (80%) and taste (73%) were better since using e-cigarettes and none reported that these were worse. Although people whose e-cigarette use completely replaced smoking were more likely to experience improvements in health and smoking caused symptoms, most people who substituted e-cigarettes for even some of their cigarettes experienced improvements.⁷⁴ Although this study was not published in a peer-reviewed journal, it still provides valuable insight into the potential impact of e-cigarettes on the health of individual smokers.
- The International Journal of Environmental Research and Public Health published a study comparing how e-cigarette vapor impacts heart cells compared to cigarette smoke.⁷⁵ More specifically, using a standardized ISO protocol, the cytotoxic potential of the vapor of 20 e-liquid samples was tested and compared to that of cigarette smoke extracted from three combustible tobacco cigarettes. The extracts, undiluted (100%) and in four dilutions (50%, 25%, 12.5%, and 6.25%), were applied to myocardial cells (H9c2); percent-viability was measured after a 24 hour incubation period. According to ISO

⁷⁴ See K. Heavner, et al., *Electronic cigarettes (e-cigarettes) as potential tobacco harm reduction products: Results of an online survey of e-cigarette users* (2009), <http://tobaccoharmreduction.org/wpapers/011v1.pdf>.

⁷⁵ See G. Romagna, Alliffranchini E, Bocchietto E, Todeschi S, Esposito M, Farsalinos KE., *Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract*. 25(6) *Inhal Toxicol*. 354-61 (2013), abstract available <http://www.ncbi.nlm.nih.gov/pubmed/23742112>.

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10993-5 protocol definition, viability of <70% was considered cytotoxic. The cigarette smoke extract showed cytotoxic effects at extract concentrations above 12.5%, while only 2 e-liquid samples were cytotoxic at 100% and 50% extract concentrations and one was cytotoxic at 100% extract concentration only. The study authors concluded that while some e-cigarette vapor samples have cytotoxic properties on cultured cardiomyoblasts, associated with the production process and materials used in flavorings, all e-cigarette vapor extracts were significantly less cytotoxic compared to cigarette smoke extracts. The flavorings that demonstrated cytotoxicity were natural extracts of tobacco leaf, and to a lesser extent, natural extract of coffee.

- A 2012 study was conducted to assess the content of the aromatic liquid mixture and its vapor and the Particulate Matter (PM) emissions of an Italian brand of e-cigarette and to compare its PM emissions with a conventional cigarette.⁷⁶ The main components of the liquid were: Propylene glycol (66%) and glycerine (24%), while the flavoring substances comprised less than 0.1%. The same substances were detected in the vapor in similar proportions. Fine and ultrafine PM emissions were higher for the conventional versus the e-cigarette (e.g.: PM10=922 vs 52 microg/m³; PM1=80 vs 14 microg/m³). The researchers found that the e-cigarette seems to give some advantages when used instead of the conventional cigarette, but more studies are needed. More specifically, the researchers found that e-cigarette use could help smokers to cope with some of the rituals associated with smoking gestures and to reduce or eliminate tobacco consumption avoiding passive smoking.
- A 2012 study evaluated the acute effect of active and passive e-cigarette and tobacco cigarette smoking on complete blood count (CBC) markers in 15 smokers and 15 never-smokers, respectively.⁷⁷ Researchers placed smokers under the following conditions: a control session, an active tobacco cigarette smoking session, and an active e-cigarette smoking session. In addition, researchers placed never-smokers under the following conditions: a passive tobacco cigarette smoking session and a passive e-cigarette smoking session. Researchers found that CBC indices remained unchanged during the control session and the active and passive e-cigarette smoking sessions (P>0.05). Active and

⁷⁶ See RM Pelligrino *et al.*, *Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM)*, 24(4) Ann Ig.279-288 (2012), abstract <http://www.ncbi.nlm.nih.gov/pubmed/22913171>.

⁷⁷ See AD Flouris *et al.*, *Acute effects of electronic and tobacco cigarette smoking on complete blood count*, 50(10) Food Chem Toxicol. 3600-3603 (2012), abstract <http://www.ncbi.nlm.nih.gov/pubmed/22858449>.

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passive tobacco cigarette smoking increased white blood cell, lymphocyte, and granulocyte counts for at least one hour in smokers and never smokers ($P < 0.05$). Accordingly, the researchers concluded that acute active and passive smoking using the e-cigarettes tested in this study did not influence CBC indices in smokers and never smokers, respectively. In contrast, the researchers noted, acute active and passive tobacco cigarette smoking increase the secondary proteins of acute inflammatory load for at least one hour.

- Researchers concluded that e-cigarettes generate smaller changes in lung function after assessing the acute impact of active and passive e-cigarette smoking on serum cotinine and lung function as compared to active and passive tobacco cigarette smoking.⁷⁸ Specifically, fifteen smokers (≥ 15 cigarettes/day; seven females; eight males) underwent a control session, an active tobacco cigarette (their favorite brand) smoking session and an active e-cigarette smoking session. 15 never-smokers (seven females; eight males) underwent a control session, a passive tobacco cigarette smoking session and a passive e-cigarette smoking session. Serum cotinine, lung function, exhaled carbon monoxide and nitric oxide were assessed. Electronic cigarettes and tobacco cigarettes generated similar effects on serum cotinine levels after active and passive smoking. Neither a brief session of active e-cigarette smoking nor a one hour passive e-cigarette smoking significantly affected the lung function. In contrast, active but not passive tobacco cigarette smoking undermined lung function.
- A 2012 study compared the effects of e-cigarette vapor and cigarette smoke on indoor air quality.⁷⁹ Researchers assessed the potential health impacts relating to the use of e-cigarettes through a series of studies using e-cigarettes and standard tobacco cigarettes. Researchers vaporized four different high nicotine e-liquids in two sets of experiments by generic 2-piece e-cigarettes to collect emissions and assess indoor air concentrations of common tobacco smoke by products. Tobacco cigarette smoke tests were conducted for comparison. Researchers compared pollutant concentrations between e-cigarette vapor and tobacco smoke samples. Pollutants included VOCs, carbonyls, PAHs, nicotine, TSNAs, and glycols. From these results, researchers conducted risk analyses based on

⁷⁸ See AD Flouris, *Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function*, 25(2) *Inhal Toxicol.* 91-101 (2013), abstract <http://www.ncbi.nlm.nih.gov/pubmed/23363041>.

⁷⁹ See T.R. McAuley *et al.*, *Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality*, 24(12) *Inhal Toxicol.* 850-857 (2012), abstract <http://informahealthcare.com/doi/abs/10.3109/08958378.2012.724728>.

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dilution into a 40 m³ room and standard toxicological data. The non-cancer risk analysis revealed “No Significant Risk” of harm to human health for vapor samples from e-liquids (A-D). In contrast, for tobacco smoke, researchers noted that most findings exceeded risk limits indicating a condition of “Significant Risk” of harm to human health. With respect to the cancer risk analysis, researchers noted that no vapor sample from e-liquids A-D exceeded the risk limit for either children or adults. The tobacco smoke sample approached the risk limits for adult exposure. The study concluded that for all byproducts measured, e-cigarettes produce very small exposures as compared to tobacco cigarettes. The study demonstrated that no apparent risk to human health results from e-cigarette emissions based on the compounds analyzed.

- A 2011 study assessed the safety of certain cigalike e-cigarettes.⁸⁰ Specifically, researchers examined 32 smokers who consume more than 20 tobacco cigarettes daily. The cartridge of an e-cigarette tested contains 0.25 g of glycerin aqueous solution. Researchers asked each study participant to consume one cartridge per day (more than 150 puffs per day) for 4 weeks. Following the treatment, researchers noted no abnormal changes in blood pressure, hematological data, or blood chemistry, nor any severe adverse events. Although researchers did detect a trace amount of acrolein in the vapor collected from a single cartridge,⁸¹ it was less than the minimum amount in the mainstream smoke from a single tobacco cigarette. Importantly, researchers noted that during the use of the electronic cigarette, participants’ daily consumption of tobacco cigarettes decreased significantly. Researchers concluded that electronic cigarettes containing glycerin aqueous solution may be a safe alternative to cigarette smoking.
- A 2011 study published in the Journal of Public Health Policy concluded that e-cigarettes “dramatically [expand] the potential for harm reduction strategies to achieve substantial health gains.”⁸² Researchers reviewed 16 studies that characterized the components of e-

⁸⁰ See Miura K, Kikukawa Y, Nakao T, Tokai H, Izumi Y, Fujii H, Hojo, T. *Safety Assessment of Electronic Cigarettes in Smokers*. 55(1) SEIKATSU EISEI (Journal of Urban Living and Health Association) 59-64 (2011).

⁸¹ This is because cartridges like these will not be able to deliver 150 puffs without going dry, and thus decomposing the glycerin.

⁸² See Cahn, Zachary and Michael Siegel, *Electronic cigarettes as a harm reduction strategy for tobacco control: A step forward or a repeat of past mistakes?*, 32 Journal of Public Health Policy 16-31 (2011), available online at: <http://www.palgrave-journals.com/jphp/journal/v32/n1/abs/jphp201041a.html>.

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cigarette liquid and vapor using gas chromatography mass spectrometry and determined that e-cigarettes are “a much safer alternative to tobacco cigarettes.”

- In a 2014 BMC Public Health research article, a researcher concluded that there is currently no evidence that exposure to e-cigarette vapor would warrant health concerns under current workplace safety standards.⁸³ The researcher extracted more than 9,000 observations of exposure to the aerosols and liquids from electronic cigarettes by reviewing peer reviewed and “grey” literature available on the chemistry of aerosols and liquids used in electronic cigarettes, then compared the exposure levels to Threshold Limit Values (TLV) for workplace exposure. Specifically, the researcher calculated the concentrations of the ingredients/contaminants in the “personal breathing zone,” either based on measured levels of specific compounds in aerosols or using worst case assumptions regarding the chemical content of aerosol and liquids as well as behavior of vapors. These concentrations were then compared to the 2013 Threshold Limit Values (TLVs) from the American Conference of Governmental Industrial Hygienists to establish whether the exposure levels presented a health concern. The researcher determined that there is no evidence that vaping produces inhalable exposures to aerosol contaminants at levels of public health concern when evaluated against standards for workplace exposure. Most of the predicted exposures were less than one percent of TLV. Predicted exposures to acrolein and formaldehyde were less than five percent of TLV.
- Unlike cigarettes, e-cigarettes are not a source of combustion toxicants. Researchers measured several markers of secondhand exposure, including nicotine, aerosol particles, carbon monoxide, and volatile organic compounds in an exposure chamber by generating e-cigarette vapor from multiple brands of e-cigarette.⁸⁴ The results showed that e-cigarette vapor is a source of second hand exposure to nicotine, but at 10 times lower concentrations than from secondhand cigarette smoke. Of note, secondhand exposure to nicotine has not been implicated as a cause for any adverse health effect and cannot lead to addiction.

⁸³ Burstyn, Igor, *Peering Through the Mist: Systemic Review of What the Chemistry of Contaminants in Electronic Cigarettes Tells Us about Health Risks*, 14 BMC Public Health 18 (2014), available <http://www.biomedcentral.com/content/pdf/1471-2458-14-18.pdf>.

⁸⁴ See Jan Czogala, PhD, *et al.*, *Secondhand Exposure to Vapors From Electronic Cigarettes*, 16(6) Nicotine Tob Res 655-662 (2014), available online at <http://ntr.oxfordjournals.org/content/16/6/655>.

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- A 2012 study identified and quantified the chemicals released on a closed environment from the use of e-cigarettes (ClearStream-AIR).⁸⁵ Researchers conducted this study in a 60m³ closed-room. Researchers organized two 5-hour sessions, the first using 5 smokers and the second using 5 users of e-cigarettes. Between sessions, the room was cleaned and ventilated for 65 hours. Smokers used cigarettes containing 0.6mg of nicotine while e-cigarette users used commercially available liquid (FlavourArt) with nicotine concentration of 11mg/ml. Researchers measured total organic carbon (TOC), toluene, xylene, carbon monoxide (CO), nitrogen oxides (NOx), nicotine, acrolein, poly-aromatic hydrocarbons (PAHs) glycerin and propylene glycol levels on the air of the room. Researchers observed that during the smoking session, 19 cigarettes were smoked, administering 11.4 mg of nicotine (according to cigarette pack information). During the e-cigarette session, researchers noted that 1.6 ml of liquid was consumed, administering 17.6 mg of nicotine. During the smoking session, researchers found: TOC=6.66 mg/m³, toluene=1.7 µg/m³, xylene=0.2 µg/m³, CO=11 mg/m³, nicotine=34 µg/m³, acrolein=20 µg/ml and PAH=9.4 µg/m³. No glycerin, propylene glycol and NOx were detected after the smoking session. During the e-cigarette session, researchers found: TOC=0.73 mg/m³ and glycerin=72 µg/m³. No toluene, xylene, CO, NOx, nicotine, acrolein or PAHs were detected on room air during the e-cigarette session. The researchers concluded that passive vaping is expected from the use of e-cigarettes, but the quality and quantity of chemicals released to the environment from e-cigarettes are far less harmful for human health as compared to regular tobacco cigarettes. Researchers noted that probable reasons for the difference in results are: evaporation instead of burning, absence of several harmful chemicals from the liquids and absence of sidestream smoking from the use of the e-cigarette.
- In an article published in the Critical Reviews in Toxicology, researchers reviewed the toxicological profiles of propylene glycol (PG), dipropylene glycol (DPG), tripropylene glycol (TPG) and polypropylene glycols (PPG; including tetra-rich oligomers) are collectively reviewed, and assessed considering regulatory toxicology endpoints.⁸⁶ The authors found that the metabolism of these compounds share common pathways, justifying a read-across approach to describing expected hazard potential from data gaps that may exist for specific oligomers, and a consistent toxicity profile. None of the

⁸⁵ See Romagna, G., et al., *Characterization of chemicals released to the environment by electronic cigarettes use*, (2012), available online at: http://clearstream.flavourart.it/site/wp-content/uploads/2012/09/CSA_ItaEng.pdf.

⁸⁶ See Fowles, Jeff, et al., *A toxicological review of the propylene glycols*, 43(4) Critical Reviews in Toxicology 363-390 (2013).

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glycols reviewed presented evidence of carcinogenic, mutagenic or reproductive/developmental toxicity potential to humans. The pathologies reported in some animal studies either occurred at doses that exceeded experimental guidelines, or involved mechanisms that are likely irrelevant to human physiology and therefore are not pertinent to the exposures experienced by consumers or workers. The authors concluded that the existing safety evaluations of the FDA, USEPA, NTP and ATSDR for these compounds are consistent and are evidence that the propylene glycols present a very low risk to human health.

- A laboratory study presented at the annual meeting of the Society of Toxicology on March 24-27, 2014 provides important new evidence that electronic cigarettes have the potential to deliver nicotine with a high degree of relative safety.⁸⁷ Specifically, the study reports that a high-technology brand of electronic cigarette (VUSE) delivers an aerosol that has no detectable carcinogens or metals - compounds that were of concern in a number of other e-cigarette brands. In the study, researchers from R.J. Reynolds Tobacco Company and the Eurofins-Lancaster Laboratories in Winston-Salem examined the constituents in the aerosol produced by VUSE electronic cigarettes. Of particular concern were a number of carcinogens, metals, and volatile compounds found in previous studies of different electronic cigarette brands. The study chromatographically profiled the chemical constituents of VUSE aerosol. The study reported that chemicals including tobacco-specific nitrosamines, carbonyls, metals, volatile organic compounds, poly-aromatic amines, polyaromatic hydrocarbons were all below either the limit of detection or limit of quantification of the laboratory methods used. In contrast, most of these compounds were detected in tobacco cigarettes in very high levels. The study concluded that the composition of VUSE aerosol is much less complex than that of tobacco smoke, that the main compounds detected are those predicted to be present (i.e., those present in the e-liquid), and that none of the toxicants of specific concern were detectable in the electronic cigarette aerosol.

Accordingly, based on growing evidence from around the world, there is no doubt that e-cigarettes and the e-liquid used in them are demonstrably less harmful for the individual consumer compared tobacco leaf-containing products, especially combusted products. Moreover, compared to the early cigalike models, ARPVs are less harmful for individual consumers because they are better designed, incorporate numerous safety features and provide

⁸⁷ See Theophilus EH, *et al.* VUSE electronic cigarette aerosol characterization (poster). Presented at the Annual Meeting of the Society of Toxicology, March 24-27, 2014.) Further discussion available at: <http://tobaccoanalysis.blogspot.com/2014/03/laboratory-study-shows-no-detectable.html>.

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more consistent and effective aerosol/nicotine delivery. We examine the “public health” impact of these products below.

b. Electronic Cigarettes Have a Positive Population Level “Public Health” Impact As The Evidence Indicates These Products are Contributing To the Declining Smoking Rate

Not only are e-cigarettes and the e-liquids used in them dramatically less harmful for individual tobacco users compared to tobacco-leaf products, they also provide a net positive population level “public health” impact. Specifically, as these products become more prevalent, the evidence that their general availability is *not* causing the smoking rate to increase further supports that FDA need not require individual companies affirmatively demonstrate that each of their products provides a public health benefit.

Cigarette smoking rates in the U.S. have fallen considerably since the introduction of e-cigarettes to the market. The Centers for Disease Control and Prevention (CDC) announced last year that the overall smoking rate declined for the first time in several years to 18% of the population from 20-21%, where it had plateaued for several years.⁸⁸ Furthermore, new data are demonstrating that youth smoking rates reached a *record low* in 2013.⁸⁹

Despite these trends, there is a growing, although unfounded, concern that e-cigarettes are acting as a “gateway” to cigarette use, particularly among youth. In this regard, FDA cited in its proposed Deeming Regulation the CDC’s much publicized National Youth Tobacco Survey (NYTS), which indicated that the percentage of students from grades six through 12 that had used an e-cigarette doubled to 6.8% from 3.3% in 2012. While the media has portrayed this as evidence that e-cigarettes are addicting new youth to tobacco, the reality is that nine out of 10 of the high school students in that survey who reported using e-cigarettes in the previous month were *already cigarette smokers*.⁹⁰ Further supporting the fact that these products are not acting

⁸⁸ See “Current Smoking” section in *Early Release of Selected Estimates Based on Data From the 2012 National Health Interview Survey*, Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), June 18, 2013, available online at http://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201306_08.pdf.

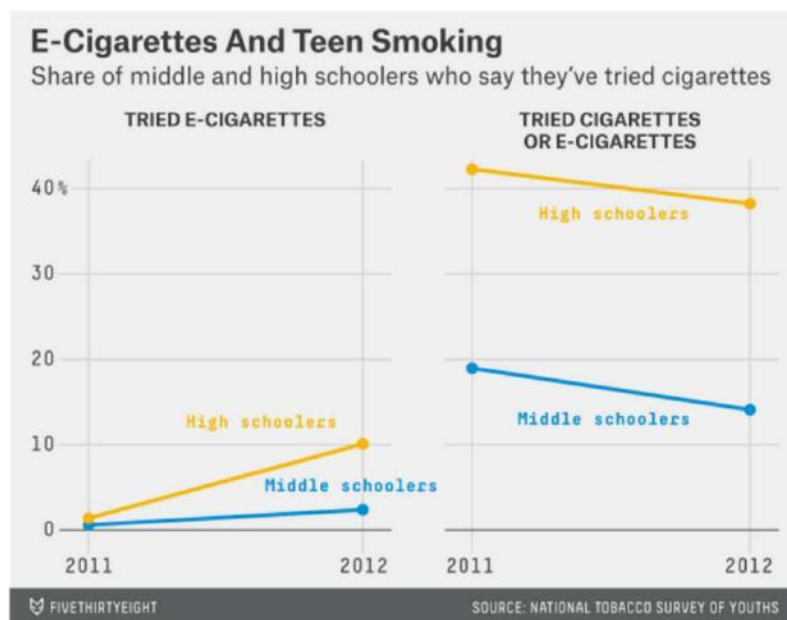
⁸⁹ See University of Michigan News, *Teen Smoking Continues to Decline in 2013*, available online at: http://monitoringthefuture.org/pressreleases/13cigpr_complete.pdf.

⁹⁰ See Sullem, Jacob, *CDC Belatedly Reveals That Smoking By Teenagers Dropped While Vaping Rose*, Forbes.com (November 20, 2013), available online at:

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as a gateway to cigarette smoking is the fact that only 0.6 percent of students in the survey reported having tried e-cigarettes and *not* regular cigarettes. Moreover, while the number of students who have “ever tried”⁹¹ an e-cigarette may have increased, it is necessary to consider that the share of students who reported trying *any* type of cigarette (combustible cigarettes or e-cigarettes) declined between 2011 and 2012:⁹²



Placed in the proper context, the NYTS actually demonstrates that e-cigarettes can be a tool for tobacco harm reduction. The dramatic decline in both overall and youth smoking rates corresponds directly with the increase in e-cigarette use over the last few years, demonstrating

(...continued)

<http://www.forbes.com/sites/jacobsullum/2013/11/20/cdc-belatedly-reveals-that-smoking-by-teenagers-dropped-while-vaping-rose/>.

⁹¹ Of course, the fact that some youth may be experimenting with e-cigarettes should not come as a major surprise to anyone who has been a teenager. There is nothing to indicate that the youth who have “ever tried” an e-cigarette have or will become regular users of these products.

⁹² See Oster, Emily, *What Do We Really Know About the Safety of E-Cigarettes?*, available online at: <http://fivethirtyeight.com/features/what-do-we-really-know-about-the-safety-of-e-cigarettes/#fn-1>.

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the public health benefit these products provide. For this reason, until there is data that clearly shows the opposite, *i.e.*, that the availability of e-cigarettes is actually *increasing* cigarette smoking rates, FDA should not implement regulations that could alter the status quo. There is a growing body of evidence in the public literature that demonstrate that e-cigarettes and the e-liquid used in them are having a net positive population-level impact by providing a significantly less harmful source of nicotine for current tobacco users and cigarette smokers, and are not having the “gateway” effect to cigarettes feared by many.

**i. Compared to Cigalike Electronic Cigarettes,
Advanced Refillable Personal Vaporizers
Provide a Greater Benefit to the Public Health,
Especially Because They May be Used with
Flavored E-Liquids**

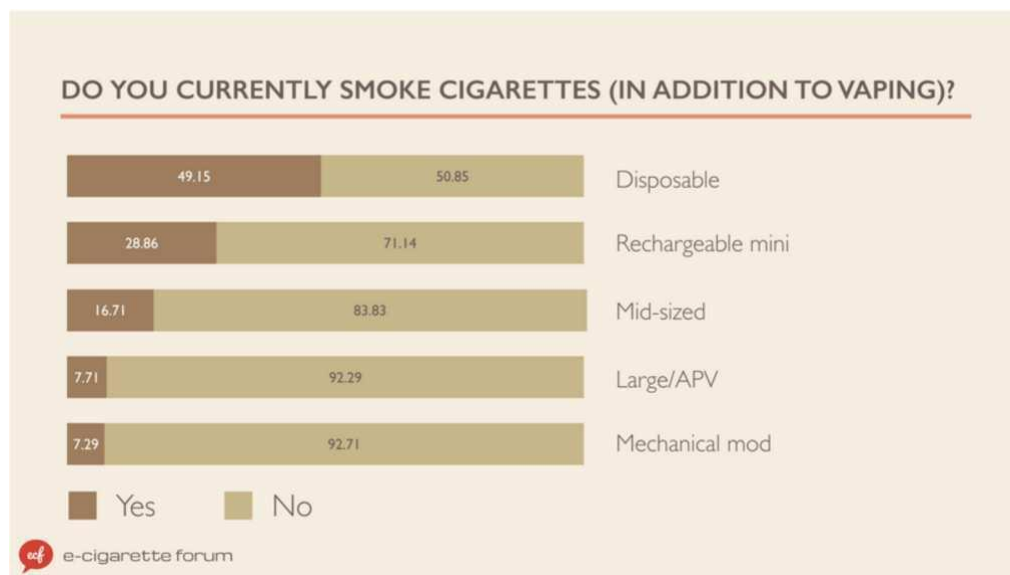
As noted above, the cigalike e-cigarette models that have been on the market since the early days of the industry are, for the most part, rudimentary, and do not incorporate safety features or provide consistent aerosol/nicotine delivery. Many cigarette smokers looking to make the switch to a less harmful recreational source of nicotine find cigalikes to be less satisfying than the “real thing,” which, in turn, often results in “dual use” with cigarettes, or complete relapse to smoking. ARPVs provide a public health benefit compared to cigalikes because they provide a better vaping experience for adult consumers, many of whom are former smokers. Numerous studies and consumer preference surveys have shown that ARPVs are better at delivering nicotine and keeping former smokers satisfied while they transition to less harmful sources of nicotine (compared to combustible cigarettes). For example, a research team lead by Dr. Konstantinos Farsalinos measured the amount of nicotine delivered to the bloodstream by various e-cigarette devices.⁹³ Specifically, plasma nicotine levels were measured in experienced e-cigarette users using a first generation cigalike and a new-generation ARPV device. After one hour of vaping using an 18 mg/mL nicotine-containing e-liquid, plasma nicotine levels were observed to be 35% to 72% higher in ARPV users compared to the cigalike users. While the ARPV device delivered nicotine more efficiently compared to the cigalike, it still did so at a

⁹³ See Farsalinos, *et al.*, *Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices*, Scientific Reports 4, Article number: 4133, available online at: <http://www.nature.com/srep/2014/140226/srep04133/full/srep04133.html>. For purposes of full disclosure, please note that this study was funded by AEMSA. The study was completely investigator-initiated and investigator-driven, however. AEMSA had no involvement in the study design, data collection, analysis and interpretation, writing or approving the manuscript and decision to submit the manuscript for publication. The study was presented in part during a meeting with the FDA Center for Tobacco Products by Dr. Farsalinos.

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much slower rate compared to tobacco cigarettes. Overall, the amount of nicotine delivered using the e-cigarette devices was about one-third to one-fourth the amount delivered by traditional tobacco cigarettes after five minutes of use.⁹⁴ This is one of the reasons ARPV users tend to be former smokers who, instead of going back to smoking, transitioned to the more advanced products when the cigalike brands failed to meet their needs.

ARPVs are also less likely to result in dual use with tobacco cigarettes. In a recent, comprehensive survey of 10,000 vapers conducted by the E-Cigarette Forum (ECF), 78% of the e-cigarette users surveyed that continue to smoke cigarettes were using rechargeable or disposable cigalike products, compared to only 8% of users of large ARPV devices:⁹⁵



⁹⁴ The researchers further noted that the use of 18 mg/mL nicotine-concentration liquid probably compromises ARPV's effectiveness as smoking substitutes and supported the need for higher levels of nicotine-containing liquids (approximately 50 mg/ml) in order to deliver nicotine more effectively and approach the nicotine-delivery profile of tobacco cigarettes.

⁹⁵ See McLaren, Neil, *Vaping.com Big Survey 2014 - Initial Findings General*, (2014), available <http://vaping.com/data/vaping-survey-2014-initial-findings>. This survey was conducted in late June and early July 2014. Of the more than 10,000 members of E-Cigarette Forum, 78 percent of whom live in the United States. Their ages ranged from 18 to "65 and over," with 74 percent between 22 and 54.

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The overwhelming majority of ARPV users (92.29%), mechanical mods (92.71%) and mid-sized personal vaporizers (83.83%) in this survey have completely transitioned to vaping, and no longer smoke cigarettes. Cigalike vapers were far more likely to continue smoking than those who graduated to the more advanced personal vaporizers.

1. Flavored E-liquids Are a Public Health Benefit

One of the primary reasons why ARPV users are so much less likely to engage in dual use or revert to smoking is the fact that they are used in conjunction with refillable e-liquids that come in a variety of flavors and nicotine concentrations, allowing adult consumers to tailor their vaping experience to fit their needs. As discussed in Section IV above, there are thousands of e-liquid manufacturers and vape shops across the country which, in turn, produce tens of thousands of individual e-liquid products. The fact that e-liquids come in such a wide variety of flavors other than tobacco and menthol is the primary reason why vapers continue to vape rather than smoke.

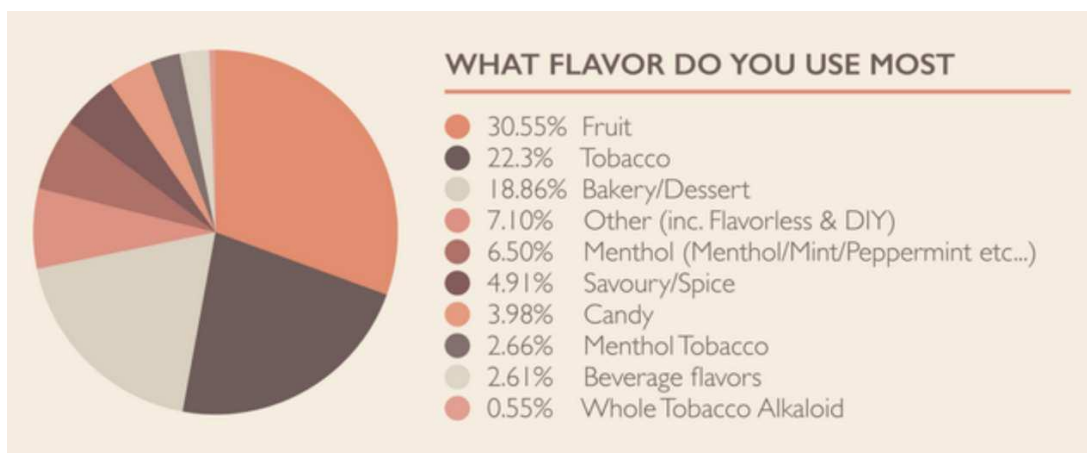
To better understand the impact that flavors have on e-cigarette users, a research team led by Dr. Farsalinos conducted a survey of 4,618 dedicated vapers.⁹⁶ Of the 4,515 participants that reported their current cigarette smoking status, the overwhelming majority (91.1%) were former smokers (*i.e.*, vapers who have transitioned completely to e-cigarettes from combustible cigarettes). Of the remaining current smokers (*i.e.*, vapers that continue to smoke cigarettes), they had, on average, reduced their cigarette consumption from 20 to 4 units per day. Both subgroups (former smokers and current smokers) had a median smoking history of 22 years and had been using e-cigarettes for 12 months. On average, the participants were using three different types of e-liquid flavors on a regular basis, with former smokers switching between flavors more frequently, compared to current smokers. Specifically, 69.2% of the former smokers reported using different e-liquid flavors on a daily basis or during the day. Fruit flavors were more popular at the time of participation, while tobacco flavors were more popular at initiation of e-cigarette use. In other words, smokers making the transition to vaping were like to initially make the switch using tobacco flavored e-liquids, but then began enjoying other flavors. On a scale from 1 (not at all important) to 5 (extremely important) participants answered that variability of flavors was “very important” (score = 4) in their effort to reduce or quit smoking. The majority reported that restricting flavor variability will make e-cigarettes less enjoyable and more boring, while 48.5% mentioned that it would increase craving for combustible cigarettes. Nearly 40%

⁹⁶ See Farsalinos, K., *et al. Impact of Flavour Variability on Electronic Cigarette Use Experience: An Internet Survey*, 10(12) Int. J. Environ. Res. Public Health 7272-7282 (2013), available online at: <http://www.mdpi.com/1660-4601/10/12/7272>.

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said that it would have been less likely for them to reduce or quit smoking if not for flavored e-liquids. The number of flavors used was independently associated with smoking cessation.⁹⁷

This public health benefit of e-liquid flavors was also recently reinforced by ECF's survey of 10,000 vapers noted above. When asked which e-liquid flavor they used most, only about 25% of the participants indicated tobacco or menthol tobacco. This means that three-quarters of the adult e-cigarette users surveyed actually prefer flavors *other* than tobacco, including fruit (31 percent), bakery/dessert (19 percent), and savory/spice (5 percent)⁹⁸:



Approximately 65.5% of the former smokers surveyed consider e-liquid flavors important in helping them transition completely to vaping and away from smoking.

FDA itself has recognized the importance of having palatable cigarette alternatives available in order to reduce harm. Specifically, in the case of the Nicorette® gum, FDA has determined that a variety of flavors such as White Ice Mint®, Cinnamon Surge™, Fruit Chill™,

⁹⁷ Of course, as noted above, e-liquids are not marketed for use in smoking cessation or as a nicotine replacement therapy, but only for recreational use. Any smoking cessation or reduced cigarette consumption resulting from the use of e-liquids or e-cigarettes generally is a corollary benefit of these products.

⁹⁸ See *Vaping.com Big survey 2014 - initial findings general*, available online at: <http://vaping.com/data/vaping-survey-2014-initial-findings>. See also *Survey Shows Adults Who Use E-Cigarettes To Quit Smoking Prefer Supposedly Juvenile Flavors*, Forbes.com, (2014), available online at: <http://www.forbes.com/sites/jacobsullum/2014/07/17/survey-shows-adults-who-use-e-cigarettes-to-quit-smoking-prefer-allegedly-juvenile-flavors/>.

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FreshMint™ and Mint provide a more palatable alternative for adult smokers and do not present a significant risk for abuse.⁹⁹ In the case of Nicorette, the Agency clearly determined that the benefit of having a variety of palatable/flavored options outweighed the risk that the flavors might attract adolescents or non-smokers to the over-the-counter product, or otherwise lead to the product being abused. There are, in fact, many consumable products on the market today that are intended for adults and are offered in fruity, candy and other flavors, such as flavored alcohol beverages.¹⁰⁰

Although e-cigarettes and e-liquids are recreational use products and not intended to be smoking cessation devices (as noted above, the fact that smokers may use these products to quit smoking is a corollary benefit – no explicit smoking cessation claims are being made by AEMSA members), the same principle applies. Non-tobacco e-liquid flavors assist e-cigarette users to associate their nicotine fix with a new taste, helping them transition away from smoking and creating an additional barrier to relapse, as returning to combustible cigarettes would mean getting used to the burning flavor of tobacco smoke again. Alternatively, the tobacco-flavored e-liquids could trigger an urge to smoke cigarettes. Ultimately, as cigarette use continues to decrease, without sufficient scientific data to support a product standard restricting or banning the use of characterizing flavors in e-cigarettes and e-liquids, the Agency must proceed with extreme caution before promulgating any such standard.¹⁰¹ If FDA were to move too quickly in this regard, such a move could be detrimental to the public health, as smokers who prefer e-cigarette/e-liquid flavors would have no palatable alternatives to turn to. Such smokers could switch back to harmful cigarettes.

We further note that ARPVs are not likely to increase initiation of tobacco or cigarette use because the often large and bulky devices lack the “coolness” factor of cigalikes as they are

⁹⁹ See <http://www.nicorette.com/nicorette-gum> (“Quitters agree — Nicorette Gum tastes great. Choose from six sugar-free flavors: White Ice Mint®, Cinnamon Surge™, Fruit Chill™, FreshMint™, Mint and Original.”)

¹⁰⁰ See, for example, Smirnoff vodka flavors: <http://www.smirnoff.com/en-us/newmain/vodka-drinks/drink-products/#axzz38s0TZob7>.

¹⁰¹ Moreover, any ban on flavored e-liquids would likely result in an unintended ban of *all* electronic cigarette products. See *Glantz and Colleagues Essentially Call for a Ban on Electronic Cigarettes: Banning Flavors Would Ban All Existing E-Cigarettes*, by Dr. Michael Siegel, available online at <http://tobaccoanalysis.blogspot.com/2014/06/glantz-and-colleagues-essentially-call.html>.

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not intended to mimic the look and feel of a traditional cigarette.¹⁰² Additionally, many of these products can also be prohibitively expensive to assemble (costing hundreds of dollars), making it much more unlikely that adolescents will initiate use with these products.

AEMSA agrees that preventing adolescents from accessing these products is paramount, but the growing body of evidence that indicates flavored e-liquids used in ARPVs may actually be providing a public health *benefit* to adults simply cannot be ignored. AEMSA's position is that manufacturers should make clear that their e-liquid products are not intended for use by anyone under the legal smoking age, and agrees that the marketing materials available online or in vape shops should not be available to minors. Manufacturers should implement robust online age-verification systems that will verify the age of online purchasers using either official government identification or verification through a reputable credit agency. AEMSA also encourages brick-and-mortar e-liquid vendors to ensure that the age of any in-person purchasers under the age of 26 is properly verified. AEMSA supports banning sales of e-liquids to minors.

Accordingly, for the reasons noted above, ARPVs provide a greater public health benefit than cigalike e-cigarettes because they provide better and more consistent nicotine/aerosol delivery, and the variety of refillable e-liquid flavors help smokers disassociate their habit with the taste of tobacco/combustion.

ii. Evidence Demonstrating that the Availability of E-Cigarettes and E-Liquids, as a Class of Products, is Having a Positive Population-Level Impact

As noted above, there is a growing body of evidence in the public literature that demonstrates that, generally, the availability of e-cigarettes and the e-liquids used in them are having a net positive population-level impact by providing a significantly less harmful source of nicotine for current tobacco users and cigarette smokers, and are not having the “gateway” effect to cigarettes feared by many.

The available evidence strongly suggests e-cigarettes are effective harm-reduction tools that help some smokers reduce or quit smoking. We highlight some of these studies below:

¹⁰² See <http://www.forbes.com/sites/jacobsullum/2014/07/17/survey-shows-adults-who-use-e-cigarettes-to-quit-smoking-prefer-allegedly-juvenile-flavors/> (“Refillable vaporizers, available mainly online or in specialized outlets, are less likely to interest teenagers than the cheaper “cigalikes” sold in supermarkets and convenience stores.”).

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- A recent study in England published in the journal *Addiction* found that smokers trying to quit were substantially more likely to succeed if they used e-cigarettes than over-the-counter therapies such as nicotine patches or gum.¹⁰³ Two randomized controlled trials were conducted and suggested that while many factors could influence real-world effectiveness, e-cigarettes can aid smoking cessation. The study included 5,863 adults who had smoked within the previous 12 months and made at least one quit attempt during that period with either an e-cigarette only (n=464), NRT bought over-the-counter only (n=1922) or no aid in their most recent quit attempt (n=3477). About a fifth of those who said they were using e-cigarettes had stopped smoking at the time of the survey, compared with about a tenth of people who had used patches and gum. More specifically, e-cigarette users were more likely to report abstinence than either those who used NRT bought over-the-counter (odds ratio 2.23, 95% confidence interval 1.70 to 2.93, 20.0% vs. 10.1%) or no aid (odds ratio 1.38, 95% confidence interval 1.08 to 1.76, 20.0% vs. 15.4%). The adjusted odds of non-smoking in users of e-cigarettes were 1.63 (95% confidence interval 1.17 to 2.27) times higher compared with users of NRT bought over-the-counter and 1.61 (95% confidence interval 1.19 to 2.18) times higher compared with those using no aid. The study authors concluded that among smokers who have attempted to stop without professional support, those who use e-cigarettes are more likely to report continued abstinence than those who used a licensed NRT product bought over-the-counter or no aid to cessation. This difference persists after adjusting for a range of smoker characteristics such as nicotine dependence.
- Another recent study from England also suggests that e-cigarettes are helping to accelerate smoking cessation, rather than hinder it.¹⁰⁴ According to this study, the prevalence of e-cigarette use began to rapidly increase in 2012 and has continued to climb steadily through the first quarter of 2014. The key finding from the study is that the annual rate of smoking cessation (that is, the percentage of current smokers who quit smoking during the past year), which had reached a low of 4.6% in 2011, increased markedly to 6.2% in 2012, 6.1% in 2013, and 8.7% for the first quarter of 2014, concomitant with the dramatic rise in e-cigarette use among these smokers. The proliferation of electronic cigarettes in England has also been associated with a dramatic

¹⁰³ See Brown, Jamie *et al.*, *Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study*, *Addiction* (forthcoming 2014), abstract available online at: <http://onlinelibrary.wiley.com/doi/10.1111/add.12623/abstract>.

¹⁰⁴ See West R, Brown J, Beard E. *Trends in electronic cigarette use in England*. Smoking Toolkit Study, London: University College London, April 4, 2014, available online at: <http://www.smokinginengland.info/latest-statistics/>.

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increase in the proportion of smokers who tried to stop in the past year (from 33.5% in 2011 to 40.3% in 2014) and an increase in the success rate for smokers who tried to quit (from 13.7% in 2011 to 21.4% in 2014). The proliferation of e-cigarettes was also associated with an acceleration in the decline in smoking prevalence. Taken together, these data suggest that the widespread use of e-cigarettes among smokers in England has advanced the degree of smoking cessation.¹⁰⁵

- A survey of more than 19,000 vapers from around the world reported in the International Journal of Environmental Research and Public Health found that almost all of the participants (99.5%) were smokers when they started vaping. Four-fifths of them had stopped smoking completely, while the rest had reduced their cigarette consumption, on average, from 20 to four per day.¹⁰⁶ This survey clearly demonstrates that e-cigarettes are reducing harm from tobacco/cigarette use and not acting as a gateway to initiation.
- Respondents from three surveys were recruited from a panel of adults in Britain to estimate prevalence and attitudes of e-cigarettes in England.¹⁰⁷ Preliminary online and face-to-face qualitative research informed the development of a smokers' survey (486 smokers who had used e-cigarettes and 894 smokers who had not). Representative samples of adults in Britain were then constructed from the panel for population surveys in 2010 (12,597 adults, including 2,297 smokers) and 2012 (12,432 adults, including 2,093 smokers), generating estimates of the prevalence of e-cigarette use and trial in Great Britain. Awareness, trial, and current use increased between 2010 and 2012; for example, current use more than doubled from 2.7% of smokers in 2010 to 6.7% in 2012. The proportion of ever-users currently using e-cigarettes was around one-third in both years. In 2012, 1.1% of ex-smokers reported current e-cigarette use, and a further 2.7% reported past use. Approximately 0.5% of never-smokers reported having tried e-

¹⁰⁵ For more analysis of this study, see *New Data from England Suggest that Electronic Cigarettes are Helping to Accelerate Smoking Cessation, Not Hinder It*, by Dr. Michael Siegel, available online at <http://tobaccoanalysis.blogspot.com/2014/04/new-data-from-england-suggest-that.html>.

¹⁰⁶ See Farsalinos, K., et al. *Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers*, 11(4) Int. J. Environ. Res. Public Health 4356-4373 (2014), abstract <http://www.ncbi.nlm.nih.gov/pubmed/24758891>.

¹⁰⁷ See Dockrell M, Morison R, Bauld L, McNeill A., *E-Cigarettes: Prevalence and Attitudes in Great Britain*, 15(10) Nicotine Tob Res. 1737-1744 (2013), abstract <http://www.ncbi.nlm.nih.gov/pubmed/23703732>.

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cigarettes. The authors concluded that there was evidence supporting the view that e-cigarette use may be a bridge to quitting and that there was little evidence of e-cigarette use among adults who had never smoked.

- In one of the first studies to examine the hypothesis that e-cigarettes are a gateway for youth to become addicted to cigarettes, Dr. Theodore Wagener from the University of Oklahoma Health Sciences Center reports being able to find only one young person who initiated nicotine use with e-cigarettes and then went on to smoke cigarettes, out of a sample of 1,300 college students.¹⁰⁸ Overall, 43 students said their first nicotine product was an e-cigarette. Of that group, only one person said they went on to smoke regular cigarettes. And the vast majority who started with e-cigarettes said they weren't currently using any nicotine or tobacco. This study provides preliminary evidence that electronic cigarettes are not currently serving as a major gateway to cigarette smoking.¹⁰⁹ Similarly, in national survey of 3,240 adults to determine use and awareness of emerging tobacco products (e.g., snus, waterpipe, dissolvable tobacco, and e-cigarettes), only 6 (six) non-smokers, out of a total of 2,000 non-smokers in the sample, had *ever* used e-cigarettes.¹¹⁰
- Self-administered written surveys assessing tobacco use behaviors were conducted in two large U.S. suburban high schools. The surveys demonstrated that, while the use of e-cigarettes increased among the students, such increase was primarily observed in

¹⁰⁸ See Goodman, Brenda, *E-Cigarettes May Not Be Gateway to Smoking: Study*, Healthday.com, (2013), available online at: <http://consumer.healthday.com/cancer-information-5/tobacco-and-kids-health-news-662/e-cigarettes-may-not-be-gateway-to-smoking-study-681597.html>.

¹⁰⁹ For more analysis of this study, see *First Study to Examine E-Cigarette Gateway Hypothesis Can Find Only One Nonsmoker Who Initiated with E-Cigs and Went on to Smoke*, by Dr. Michael Siegel, available online at <http://tobaccoanalysis.blogspot.com.au/2013/10/first-study-to-examine-e-cigarette.html>.

¹¹⁰ See McMillen R, Maduka J, Winickoff J., *Use of emerging tobacco products in the United States*. 2012 Journal of Environmental and Public Health (2012), available online at: <http://www.hindawi.com/journals/jeph/2012/989474/>. For more analysis of this study, see *National Study of Adults Can Find Only Six Nonsmokers Who Have Ever Tried Electronic Cigarettes*, by Dr. Michael Siegel, available online at <http://tobaccoanalysis.blogspot.com/2013/05/national-study-of-adults-can-find-only.html>.

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students who were already smoking cigarettes.¹¹¹ Specifically, the prevalence of e-cigarette use during the previous 30 days increased from 0.9% in February 2010 to 2.3% in June 2011 ($p = 0.009$). This is an indication of harm reduction, however, as current cigarette smokers had increased odds of e-cigarette use. When adjusted for school, grade, sex, race and smoking status, students in October 2010 and June 2011 had increased odds of past-30 day use of e-cigarettes compared to February 2010. The prevalence of e-cigarette use doubled in the sample of high school students, but current cigarette smoking was the strongest predictor of current use.

- A prospective 6-month pilot study conducted in Catania, Italy examined the effect of e-cigarettes on smoking reduction and cessation and demonstrated that the use of e-cigarettes helps smokers, not intending to quit, to remain abstinent or reduce their cigarette consumption.¹¹² The execution of this study involved monitoring possible modifications in the smoking habits of 40 regular smokers (unwilling to quit) by experimenting the 'Categoria' e-cigarette with a focus on smoking reduction and smoking abstinence. Study participants were invited to attend a total of five study visits: at baseline, week-4, week-8, week-12 and week-24. At each visit, product use, number of cigarettes smoked, and exhaled carbon monoxide (eCO) levels were all measured. In addition, smoking reduction and abstinence rates were calculated and adverse events and product preferences were also reviewed. The researchers found a sustained 50% reduction and smoking abstinence in 22/40 (55%) participants, with an overall 88% reduction in cigarettes/day. Although mouth (20.6%) and throat (32.4%) irritation, and dry cough (32.4%) were common, these side effects diminished substantially by week-24. Overall, two to three cartridges/day were used throughout the study and participants' perception and acceptance of the product was good. The researchers concluded that the use of e-cigarettes substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit.
- A 2011 study conducted in Philadelphia, Pennsylvania surveyed experienced e-cigarette users in the interest of identifying the e-cigarette products used by experienced e-cigarette users, their pattern of e-cigarette use and the impact on tobacco use. Specifically, the

¹¹¹ See Camenga, Deepa R. *et al.*, *Trends in use of electronic nicotine delivery systems by adolescents*, 39 Addictive Behaviors 338-340 (2014), abstract <http://www.sciencedirect.com/science/article/pii/S0306460313002736>.

¹¹² See Polosa, R., *et al.*, *Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study*. 11 BMC Public Health 786 (2011), available online at: <http://www.biomedcentral.com/content/pdf/1471-2458-11-786.pdf>.

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study involved face-to-face surveys of 104 experienced e-cigarette users. Researchers found that 78% of participants had not used any tobacco in the prior 30 days. Researchers noted that these e-cigarette users had previously smoked an average of 25 cigarettes per day and had tried to quit smoking an average of nine times before they started using e-cigarettes. Researchers also observed that two-thirds of e-cigarette users had previously tried to quit smoking using an FDA-approved smoking cessation NRT products. The majority of the sample in this study had used e-cigarettes daily for at least a year and three quarters started using e-cigarettes with the intention of quitting smoking. Notably, almost all participants who identified as e-cigarette users felt that the e-cigarette had helped them to succeed in quitting smoking. Researchers further noted that most participants used ARPVs which are designed to enable the atomizer to more consistently achieve a more satisfying vapor. Researchers concluded that further evidence should be collected regarding the safety and efficacy of e-cigarettes for smoking cessation and that until then, smokers should use proven treatments such as counseling and FDA-approved medicines. Nevertheless, the researchers also concluded that smokers who successfully switch to e-cigarettes, should continue vaping e-cigarettes and not revert to smoking cigarettes.¹¹³

- A 2011 internet survey in English and French examined 3,587 participants (70% former tobacco smokers, 61% men, mean age 41 years) to assess the profile, utilization patterns, satisfaction and perceived effects among users of e-cigarettes.¹¹⁴ The researchers observed that the median duration of e-cigarette use was 3 months, users drew 120 puffs/day and used five refills/day. Most participants (96%) said the e-cigarette helped them to quit smoking or reduce their smoking (92%). Reasons for using the e-cigarette included the perception that it was less toxic than tobacco (84%), to deal with craving for tobacco (79%) and withdrawal symptoms (67%), to quit smoking or avoid relapsing (77%), because it was cheaper than smoking (57%) and to deal with situations where smoking was prohibited (39%). Most ex-smokers (79%) feared they might relapse to smoking if they stopped using the e-cigarette. Users of nicotine-containing e-cigarettes reported better relief of withdrawal and a greater effect on smoking cessation than those using non-nicotine e-cigarettes. The researchers concluded that participants used e-

¹¹³ See Foulds, J. *et al.*, *Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives*, 65(10) *Int J Clin Pract.* 1037-1042 (2011), abstract <http://www.ncbi.nlm.nih.gov/pubmed/21801287>.

¹¹⁴ See Etter, J.F., *et al.*, *Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy*, 106 (11) *Addiction* 2017-2028 (2011), abstract <http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.2011.03505.x/abstract>.

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cigarettes similar to people who take nicotine replacement medications – by former smokers to avoid relapse or as an aid to cut down or quit smoking.

- A 2012 study examined the effects of the White Super e-cigarette on desire to smoke, nicotine withdrawal symptoms, attention and working memory.¹¹⁵ Researchers selected eighty-six smokers, and randomly allocated them to either: 18 mg nicotine e-cigarette (nicotine), 0 mg e-cigarette (placebo), or just hold the e-cigarette (just hold) conditions. Participants rated their desire to smoke and withdrawal symptoms at baseline (T1), and five (T2) and twenty (T3) minutes after using the e-cigarette ad libitum for 5 min. A subset of participants completed the Letter Cancellation and Brown-Peterson Working Memory Tasks. Researchers found that after 20 minutes, compared with the just hold group, desire to smoke and some aspects of nicotine withdrawal were significantly reduced in the nicotine and placebo group; the nicotine e-cigarette was superior to placebo in males but not in females. Researchers also determined that the nicotine e-cigarette also improved working memory performance compared with placebo at the longer interference intervals. There was no effect of nicotine on Letter Cancellation performance. Researchers concluded that the White Super e-cigarette alleviated desire to smoke and withdrawal symptoms 20 min after use although the nicotine content was more important for males.
- Based on data gathered from a national online study of 2,649 adults and the Legacy Longitudinal Smoker Cohort study of 3,658 adults, researchers used multivariable models to examine e-cigarette awareness, use, and harm perceptions.¹¹⁶ In the online survey, 40.2% (95% confidence interval [CI] = 37.3, 43.1) had heard of e-cigarettes, with awareness highest among current smokers. Utilization was higher among current smokers (11.4%; 95% CI = 9.3, 14.0) than in the total population (3.4%; 95% CI = 2.6, 4.2), with 2.0% (95% CI = 1.0, 3.8) of former smokers and 0.8% (95% CI = 0.35, 1.7) of never-smokers ever using e-cigarettes. The study authors concluded that awareness of e-cigarettes is high, and use among current and former smokers is evident.

¹¹⁵ See Dawkins, L., *et al.*, *The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition*, 37(8) *Addict Behav.* 970-973 (2012), abstract <http://www.ncbi.nlm.nih.gov/pubmed/22503574>.

¹¹⁶ See Pearson, J. L., *et al.*, *e-Cigarette Awareness, Use, and Harm Perceptions in U.S. adults*, 102(9) *American Journal of Public Health* 1758-1766 (2012), available online at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474361/>.

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- A study published in 2012 examined e-cigarette use among teenagers and young adults in Poland, and concluded that most youth that tried e-cigarettes and previously smoked.¹¹⁷ The researchers conducted a survey with a cluster sample of 20,240 students enrolled at 176 nationally representative Polish high schools and universities between September 2010 and June 2011. To estimate national e-cigarette prevalence among various demographic groups, researchers used population weights. In addition, researchers used multiple logistic regression to evaluate which demographic factors were independent predictors of 2 outcomes: ever use of e-cigarettes and use in the previous 30 days. The researchers found that among high school students, aged 15 to 19 years, 23.5% had ever used e-cigarettes and 8.2% had done so within the previous 30 days. Among those in universities, aged 20 to 24 years, 19.0% had ever used an e-cigarette and 5.9% had done so in the previous 30 days. In multivariate analyses that controlled for covariates, smoking cigarettes, male gender, living in an urban area, and having parents who smoke were associated with ever use of e-cigarettes. Overall, 3.2% of never smoking students reported ever use of e-cigarettes. The researchers concluded that about one-fifth of Polish youth have tried e-cigarettes; most of them had previously smoked cigarettes. This study shows the potential for harm reduction that e-cigarettes provide.
- In another study in Poland conducted in 2013, the patterns and effects of e-cigarette use and user beliefs about safety and benefits were examined.¹¹⁸ Researchers recruited 179 e-cigarette users in Poland online and asked about their smoking history, patterns of e-cigarette use, beliefs and attitudes regarding the product and information on concurrent use of conventional cigarettes. Sixty-six percent (66%) were no longer smoking conventional cigarettes and twenty-five (25%) had reduced their consumption to less than five cigarettes a day. Most participants (82%) did not think that e-cigarettes were completely safe, but correctly understood that they are less dangerous than conventional cigarettes. The study found that the participants primarily used e-cigarettes to assist their efforts to stop smoking or as an alternative to conventional cigarettes; the majority of participants reported that they successfully stopped smoking.

¹¹⁷ See Goniewicz, ML, and Zielinska Danch W., *Electronic cigarette use among teenagers and young adults in Poland*, 130(4) *Pediatrics* e879-885 (2012), abstract <http://www.ncbi.nlm.nih.gov/pubmed/22987874>.

¹¹⁸ See Goniewicz, ML, *et al.*, *Patterns of electronic cigarette use and user beliefs about their safety and benefits: an Internet survey*, 32(2) *Drug Alcohol Rev.* 133-140 (2013), abstract <http://www.ncbi.nlm.nih.gov/pubmed/22994631>.

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- A 2011 study conducted in Italy examined the association between nicotine dependence and depression in two subjects.¹¹⁹ Specifically, researchers conducted a case study of two heavy smokers with an established history of depression. Both subjects had previously attempted intensive smoking cessation programs with no success. Researchers found, however, that e-cigarette use led each to successfully quit smoking. Although the researchers acknowledge that the findings cannot be generalized, they note that high quit rates would be desirable among smokers suffering from depression (who generally respond poorly to smoking cessation efforts) and that, therefore, additional studies should be conducted to explore whether e-cigarette use should be considered as a potential tool to aid in smoking cessation.
- A 2013 U.S. population survey revealed that current smokers were more likely than never-smokers to report use of e-cigarettes.¹²⁰ Survey respondents were asked if they had heard of e-cigarettes, where they heard of e-cigarettes, whether and how often they used e-cigarettes, and why. Responses were weighted to represent the entire U.S. population. A high proportion, 75.4%, reported having heard about e-cigarettes. About 8.1% had tried e-cigarettes, and 1.4% were current users. These rates were twice those of snus (4.3% and 0.8%, respectively). Among current smokers, 32.2% had tried e-cigarettes, and 6.3% were current users. Over 80% of current e-cigarette users were non-daily users. Women were significantly more likely to have tried e-cigarettes than men. Those who had tried e-cigarettes were more likely than those who tried snus to report their products being safer than regular cigarettes (49.9% vs. 10.8%). Almost half (49.5%) of current smokers were susceptible to using e-cigarettes in the future. The study authors concluded that e-cigarettes have surpassed snus in adoption rate, even before any promotion by major tobacco companies, suggesting that the former have tapped into smokers' intuitive preference for potentially harm-reducing products, probably due to the product design.
- Researchers from the University of Geneva and the University of Auckland, New Zealand, recruited 477 volunteers from websites devoted to e-cigarettes and/or smoking

¹¹⁹ See Caponnetto, P. *et al.*, *Smoking Cessation with E-Cigarettes in Smokers with a Documented History of Depression and Recurring Relapses*, 2(3) International Journal of Clinical Medicine 281-284 (2011), available online at: <http://www.scirp.org/journal/PaperInformation.aspx?PaperID=6134#.U9kbLxCORWw>.

¹²⁰ See Zhu S-H, *et al.*, *The Use and Perception of Electronic Cigarettes and Snus among the U.S. Population*, 8(10) PLoS ONE (2013), available online at: <http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0079332&representation=PDF>.

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cessation, and followed their smoking and vaping habits over one-month (477 subjects) and one-year (367 subjects) periods.¹²¹ At the one-month mark, among the former smokers who were regular e-cigarette users, only 6% had taken up smoking again. Of those who both smoked and used e-cigarettes, 46% had quit smoking by the one-year mark. The study shows that dual use may ultimately lead to smoking cessation.

- A prospective 12-month double-blind, controlled, randomized clinical study with two different nicotine strengths of a very popular e-cigarette brand was conducted to evaluate smoking reduction, smoking abstinence and adverse events in smokers who were not otherwise intending to quit.¹²² The authors concluded that the use of e-cigarettes, with or without nicotine, decreased cigarette consumption and elicited enduring tobacco abstinence without causing significant side effects. Three hundred smokers were recruited and placed into three equal study groups: Group A received 7.2 mg nicotine cartridges for 12 weeks; Group B received 6-weeks of 7.2 mg nicotine cartridges followed by a further 6-weeks of 5.4 mg nicotine cartridges; and Group C received no-nicotine cartridges for 12 weeks. The study consisted of nine visits during which cigarette day use and exhaled carbon monoxide (eCO) levels were measured. Declines in cigarette per day use and eCO levels were observed at each study visits in all three study groups, with no consistent differences among study groups. Smoking reduction was documented in 22.3% and 10.3% at week 12 and week 52 respectively. Complete abstinence from tobacco smoking was documented in 10.7% and 8.7% at week 12 and week 52 respectively, leading to the conclusion that the use of e-cigarettes helped to reduce cigarette consumption and in some cases resulted in tobacco abstinence.
- A year-long study of 14 smokers (not intending to quit) with schizophrenia was conducted to determine impact of e-cigarettes on their smoking behavior and condition.¹²³ The study authors concluded that the use of e-cigarettes substantially

¹²¹ See Etter, JF, and Chris Bullen, *A longitudinal study of electronic cigarette users*, 39(20) Addictive Behaviors 491-494 (2014), abstract
<http://www.sciencedirect.com/science/article/pii/S0306460313003304>.

¹²² See Caponnetto P, et al., *EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study*, 8(6) PLoS One (2013), available online at
<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0066317>.

¹²³ See Caponnetto P, et al., *Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study*, 10(2) Int J Environ Res (continued ...)

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decreased cigarette consumption without causing significant side effects in chronic schizophrenic patients. Product use, number of cigarettes smoked, carbon monoxide in exhaled breath (eCO) and positive and negative symptoms of schizophrenia levels were measured. Sustained 50% reduction in the number of cigarettes per day at week 52 was shown in 50% of participants, with their median of 30 cigarettes per day decreasing significantly to 15 cigarettes per day. Sustained smoking abstinence at week 52 was observed in 2 participants with combined sustained 50% reduction and smoking abstinence in 9 participants. Overall, one to two e-cigarette cartridges per day were used throughout the study. The authors concluded that positive and negative symptoms of schizophrenia are not increased after smoking reduction/cessation in patients using e-cigarettes.

- In a study that sought to characterize e-cigarette use, users, and effects in a sample of Electronic Cigarette Company (TECC) and Totally Wicked E-Liquid (TWEL) users, the authors concluded that e-cigarettes are used primarily for smoking cessation, but for a longer duration than nicotine replacement therapy, and users believe them to be safer than smoking.¹²⁴ Respondents (1347) completed a questionnaire regarding their e-cigarette use, and 74% reported not smoking for at least a few weeks since using the e-cigarette and 70% reported a reduced urge to smoke. E-cigarettes were generally considered to be satisfying to use, elicit few side effects, be healthier than smoking, improve cough/breathing, and resulted in low levels of craving. Among ex-smokers, ‘time to first vape’ was significantly longer than “time to first cigarette,” suggesting a lower level of dependence to e-cigarettes. Ex-smokers reported significantly greater reduction in craving than current smokers although few other differences emerged between these groups. Compared with males, females opted more for chocolate/sweet flavors and liked the e-cigarette because it resembles a cigarette.
- A qualitative study was conducted to determine how e-cigarettes compare to NRTs in maintaining cigarette abstinence.¹²⁵ Using focus groups, e-cigarette users discussed their

(...continued)

Public Health 446-461 (2013), available online at: <http://www.mdpi.com/1660-4601/10/2/446/htm>.

¹²⁴ See Dawkins L, Turner J, Roberts A, Soar K., *Vaping’ profiles and preferences: an online survey of electronic cigarette users*, 108(6) *Addiction* 1115-1125 (2013), abstract <http://onlinelibrary.wiley.com/doi/10.1111/add.12150/abstract>.

¹²⁵ See Barbeau AM, Burda J, Siegel M., *Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach*, 8(1) *Addict Sci* (continued ...)

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perceptions of e-cigarette efficacy for smoking cessation compared to NRTs. The study sought to explain the popularity of these devices and to shed light on the factors which influence the efficacy of different smoking cessation products. Five themes emerged that describe users' perceptions of why e-cigarettes are efficacious in quitting smoking: 1) bio-behavioral feedback, 2) social benefits, 3) hobby elements, 4) personal identity, and 5) distinction between smoking cessation and nicotine cessation. The authors concluded that tobacco control practitioners must pay increased attention to the importance of the behavioral and social components of smoking addiction. By addressing these components, in addition to nicotine dependence, e-cigarettes appear to help some cigarette smokers transition to a less harmful replacement tool, thereby maintaining cigarette abstinence.

- In a survey study conducted across four countries (Canada, U.S., U.K. and Australia), the authors examined patterns of e-cigarette awareness, use, and product-associated beliefs among current and former smokers, concluding that e-cigarettes may have the potential to serve as a smoking cessation aid.¹²⁶ The study showed that 79.8% reported using e-cigarettes because they were considered less harmful than traditional cigarettes, 75.4% stated that they used e-cigarettes to help them reduce their smoking, and 85.1% reported using e-cigarettes to help them quit smoking.
- A study conducted in 2009 by the Northern Sweden cohort of the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) concluded that the use of e-cigarettes was a significant factor in the low prevalence of smoking, especially among younger men and women in Northern Sweden.¹²⁷

(...continued)

Clin Pract. 5 (2013), available online at: <http://www.biomedcentral.com/content/pdf/1940-0640-8-5.pdf>.

¹²⁶ See Adkison SE, et al., *Electronic nicotine delivery systems: international tobacco control four-country survey*, 44(3) Am J Prev Med. 207-215 (2013), abstract <http://www.ncbi.nlm.nih.gov/pubmed/23415116>.

¹²⁷ See Rodu B1, Jansson JH, Eliasson M, *The low prevalence of smoking in the Northern Sweden MONICA study*, 41(8) Scand J Public Health. 808-811 (2013), abstract <http://www.ncbi.nlm.nih.gov/pubmed/24052339>.

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- A 2014 study documented the prevalence of e-cigarette ever use, current use, and established use in a nationally representative survey of 2,236 current and former cigarette smokers in the U.S.¹²⁸ Participants completed a web-based survey in June 2013. The data from that survey was analyzed using multivariate logistic regression, which identified demographic and smoking-related factors associated with each use category. Researchers observed that almost half of the study participants had tried e-cigarettes (46.8%), but prevalence of established use remained low (3.8%). Researchers further observed that although trial of e-cigarettes was highest among daily smokers, it was much more likely for former smokers to identify as an established e-cigarette user. Importantly, the results demonstrated that most/all of the survey's established e-cigarette users who were also former smokers became former smokers by switching to e-cigarettes.
- A single-blind randomized trial measured the short-term effects of an e-cigarette on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects.¹²⁹ Study participants included 40 adult dependent smokers of 10 or more cigarettes per day. Researchers randomized study participants to use e-cigarettes containing 16 mg nicotine or 0 mg capsules, Nicorette nicotine inhalator or their usual cigarette on each of four study days 3 days apart, with overnight smoking abstinence before use of each product. Researchers found that over 60 minutes, participants using 16 mg an e-cigarette recorded 0.82 units less desire to smoke than the placebo e-cigarette (p=0.006). Researchers did not observe a difference in desire to smoke between the 16 mg e-cigarette and the Nicorette nicotine inhalator. Study participants found e-cigarettes to be more pleasant to use than the inhalator (p=0.016) and produced less irritation of mouth and throat (p<0.001). Researchers observed that, on average, the e-cigarette increased serum nicotine to a peak of 1.3 ng/mL in 19.6 min, the Nicorette nicotine inhalator to 2.1 ng/ml in 32 min and cigarettes to 13.4 ng/ml in 14.3 min. Researchers concluded that the 16 mg Ruyan V8 e-cigarette alleviated desire to smoke after overnight abstinence, was well tolerated among study participants, and had a pharmacokinetic profile more like the Nicorette nicotine inhalator than a tobacco cigarette.

¹²⁸ See Giovenco, Daniel P., *et al.*, *Factors Associated with E-cigarette Use, A National Population Survey of Current and Former Smokers*, Am. J. Prev. Med. (2014), abstract <http://www.ncbi.nlm.nih.gov/pubmed/24880986>.

¹²⁹ See Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M., *Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial*, 19 Tob. Control 98-103 (2010), abstract <http://tobaccocontrol.bmj.com/content/19/2/98.abstract>.

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- Three quarters of e-cigarette users surveyed in a 2012 study reported that using e-cigarettes helped them quit smoking.¹³⁰ The study participants smoked an average of 25 cigarettes per day prior to the study and tried to quit smoking an average of nine times before using e-cigarettes (two-thirds of the participants had previously tried to quit smoking using an FDA-approved smoking cessation product). The majority of the e-cigarette users involved in the study had used e-cigarettes daily for at least a year. Most of the study participants did not use the type of e-cigarette that are commonly sold, i.e., those powered by a single 3.7 volt battery; these users represented only 8% of the study participants. Two-thirds of the participants used e-cigarettes designed to enable the atomizer to achieve hotter, more intense vapor with e-liquids containing medium to high concentrations of nicotine (13 mg +). Due to the results of the survey the study authors have concluded that those who already have switched to e-cigarettes should focus on staying off cigarettes, rather than quitting e-cigarettes.
- Over two hundred smokers who had tried e-cigarettes were surveyed online to examine the effectiveness of e-cigarettes as a smoking cessation tool.¹³¹ The primary outcome of interest in the study was the point prevalence of smoking abstinence at 6 months after initial e-cigarette purchase. In summary, the point prevalence of smoking abstinence at 6 months after initial e-cigarette purchase was 31.0% (95% CI=24.8%, 37.2%). A large percentage of respondents reported a reduction in the number of cigarettes they smoked (66.8%), and almost half reported abstinence from smoking for a period of time (48.8%). The participants that reported using e-cigarettes more than 20 times per day had a quit rate of 70.0%. Of respondents who were not smoking at 6 months, 34.3% were not using e-cigarettes or any nicotine-containing products at the time. The researchers concluded that e-cigarettes are a promising smoking-cessation tool worthy of further study using more rigorous research designs.
- In an Internet study of 81 e-cigarette users in France, Canada, Belgium, and Switzerland, participants answered open-ended questions regarding their use of e-cigarettes, and

¹³⁰ See Leelavathi, M. and S. Das, *Electronic cigarettes: new kit on the rack*, 66(4) Int J Clin Pract. 417 (2012), abstract <http://www.ncbi.nlm.nih.gov/pubmed/22420500>.

¹³¹ See Siegel, MB, et al., *Electronic cigarettes as a smoking-cessation: tool results from an online survey*, 40(4) Am J Prev Med. 472-475 (2011), abstract <http://www.ajpmonline.org/article/S0749-3797%2810%2900792-0/abstract>.

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opinions regarding these products.¹³² Over half of participants (63%) were former smokers; 37% of participants were current smokers. Participants reported using e-cigarettes either to quit smoking, to reduce cigarette consumption, to avoid disturbing other people with secondhand smoke, or to be able to smoke in smoke-free places. There were numerous positive effects associated with e-cigarettes. These included reports that the products are useful in quitting cigarette smoking, and confer the benefits of abstinence from cigarette smoking (less coughing, improved breathing, better physical fitness).

Accordingly, the growing body of data establishes that e-cigarettes and the e-liquids used in them (1) provide a much less harmful alternative to tobacco leaf-containing products (especially combustible cigarettes) for current tobacco users and (2) do not have an adverse impact on smoking initiation and cessation rates (*i.e.*, the evidence indicates that the products have contributed to the continuing decline in the percentage of the population that smokes cigarettes). In particular, ARPVs provide a greater public health benefit than cigalike e-cigarettes because they are able to more consistently deliver the nicotine-containing aerosol and because of the variety of available refillable e-liquid flavors, which help smokers disassociate their habit with the taste of tobacco/combustion.

Based on the above, FDA should adopt an alternative regulatory framework for these novel products whereby individual e-cigarette and e-liquid manufacturing companies need not affirmatively demonstrate that each of their products will have a positive net-population level public health impact in their PMTAs. Rather, in order to meet the “appropriate for the protection of the public health” legal standard, such companies need only consider the impact of their product on the health of individual consumers by, for example, demonstrating that their products are compliant with established product standards, manufactured in accordance with Good Manufacturing Practices and marketed responsibly toward adult consumers.

ii. To Demonstrate Safety to the Individual Consumer, E-Cigarette and E-Liquid Manufacturing Companies Need Only Ensure that their Products Comply with Industry-Specific Product Standards and Good Manufacturing Practices

Even if FDA makes a general finding that e-cigarettes, as a class of products, provide a public health benefit and thereby removes the burden of demonstrating the population-level

¹³² Further research on e-cigarettes is urgently required, particularly with respect to the efficacy and toxicity of these devices. See Etter, JF, *Electronic cigarettes: a survey of users*, 10 BMC Public Health 231 (2010), available online at: <http://www.biomedcentral.com/content/pdf/1471-2458-10-231.pdf>.

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impact of each product from individual manufacturers, under this proposed regulatory framework, such manufacturers should still be required to show that their products are “appropriate for the protection of the public health,” but by focusing solely on the impact of their products on the health of the *individual* consumer. This can be most efficiently achieved if FDA develops science-based industry-specific product standards and Good Manufacturing Practices. AEMSA also supports full disclosure to FDA of all e-liquid ingredients (pursuant to the framework set forth in Regulatory Framework No. 4 below) as well as requirements to ensure marketing and advertising do not unduly appeal to minors.

Crafting appropriate, science-based product standards for e-cigarettes and e-liquids will be a difficult task that will take much time to develop given the complexity of the technology and our evolving understanding of the science. As such, FDA should delay the effective date of the Deeming Regulation until it is ready to promulgate product standards and GMPs for these products (via its rulemaking procedures to ensure that industry stakeholders, public health advocates and, most importantly, consumers have a say).¹³³

1. Establishing Product Standards for E-Cigarettes and E-Liquids

To ensure these products are produced in a safe manner and are not unnecessarily harmful to the health of individual consumers, FDA should work with industry (including AEMSA and the Smoke Free Alternatives Trade Association (SFATA)), the public health community and consumer protection advocates (such as the Consumer Advocates for Smoke-free Alternatives Association (CASAA)) to establish a standards-setting body whose mission will be to develop science-based¹³⁴ product standards and specifications for e-cigarettes, e-cigarette component parts and e-liquids.

¹³³ It is not uncommon for FDA to delay rulemaking until the underlying science is established. The potential regulation of menthol in cigarettes is a good example. As noted in Section II above, the Agency is currently waiting for the science to develop before promulgating a rule prohibiting or restricting the use of menthol as a characterizing flavor in cigarettes. FDA should take the same approach here and wait until it has sufficient scientific understanding to promulgate product standards and GMPs for these products. It should delay deeming these novel products to be regulated tobacco products until such time.

¹³⁴ According to FDA’s own *Strategic Plan for Regulatory Science*, the Agency’s “core responsibility is to protect consumers by applying the best possible science to its regulatory activities.” In this regard, “FDA is also responsible for advancing the public health by helping to speed innovations that provide our nation with safe and effective medicines and devices and keep
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Many other industries have benefitted from this approach, and FDA has worked with standards setting bodies in the past in this very way. For example, in 2006 FDA issued an updated list of consensus standards recognized by the Agency for use in evaluating medical devices prior to receiving premarket approval for entry. The Food and Drug Administration Modernization Act (FDAMA) of 1997 authorized the Agency to recognize standards developed in an open and transparent process, such as those developed by American National Standards Institute (ANSI)-accredited standards developing organizations, as well as the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC).¹³⁵

Ultimately, with respect to e-liquids, product standards should be designed to ensure that the ingredients used are U.S. Pharmacopeia (USP)-certified (where applicable) and are suitably pure for their intended use (*i.e.*, the amount of impurities/contaminants do not exceed specified levels), that well-known impurities such as diethylene glycol and diacetyl, among others, are not detectable at appropriately sensitive analytical detection limits using standard test procedures, and that the concentrations of nicotine and other baseline ingredients are verifiable and accurate. Child-resistant and tamper evident packaging for any e-liquid containing nicotine sold to consumers should also be mandated. Furthermore, as detailed below, GMPs for e-liquids should be established based on AEMSA's manufacturing standards to ensure these products are manufactured in a safe manner. FDA should also consider regulating these refillable e-liquids based on a combination of commercial food manufacturing and micro-brewery/winery standards.

Regarding e-cigarette devices themselves, standards should focus on the following core principles:

- The most important standard for FDA to establish is a regulatory maximum temperature limit that a vaporizer device may not exceed during operation, regardless of the e-liquid,

(...continued)

our food supply safe, while helping Americans get the accurate, science-based information they need to use medical products and consume foods to improve and maintain their health.” We recommend FDA heed its own advice, and base any decisions with respect to the regulation of e-cigarettes and e-liquids on sound, peer-reviewed science. See *Introduction: Strategic Plan for Regulatory Science*, available online at:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268098.htm>.

¹³⁵ See ANSI, *FDA Issues List of Recognized Consensus Standards for Medical Devices*, available online at:

http://www.ansi.org/news_publications/news_story.aspx?menuid=7&articleid=1190.

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airflow or heater coil used. This is critically important because the breakdown of the consumable e-liquid fluid into potentially harmful substances is primarily a function of temperature. In other words, the chemical composition of the inhaled aerosol will largely depend on the temperature to which the e-liquid and internal vaporizer components (coil) are heated. Excessive heat may result in the formation of unintended impurities/degradation compounds, such as formaldehyde. In developing temperature standards, FDA should work with industry experts to determine if there should be one maximum temperature for all products, or whether it makes sense to have multiple temperature limits for specific product types or e-liquid (*e.g.*, if the e-liquid contains propylene glycol, then the internal temperature of the device should not exceed that which could result in the formation of formaldehyde).

- Products should incorporate standard safety features including, but not limited to, auto-shut off capabilities, short-circuit protections, and “smart charging” ability,¹³⁶ over/under-charge protections, and consumer safety features to prevent abuse/misuse (*i.e.*, child-proof packaging).
- All e-cigarette devices and components shall incorporate electronic protections designed and constructed so that a short-circuit in the atomizer, improperly installed battery, incorrect battery or any reasonably foreseeable error by the consumer (*i.e.*, using unauthorized car charger) will not cause unacceptably elevated temperatures, charring, smoke or fire.
- Batteries and chargers should be designed to ensure they will not over-heat or cause electrical damage to the device.
- Electronic cigarette devices and components should be required to meet standards similar to the European Union’s Restriction of Hazardous Substances Directive 2002/95/EC (RoHS or RoHS2), which restricts the use of certain hazardous substances (*e.g.*, lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyls, polybrominated diphenyl ether) in electrical and electronic equipment.
- Standards for the manufacture and use of the various e-cigarette/ARPV component parts (*e.g.*, adapters, atomizers, cartomizers, clearomizers, batteries, chargers, tanks, endcaps, tubing, internal microprocessors/motherboards, springs, o-rings, drip-tips/mouth pieces, wicking materials, and other device components such as internal connectors, buttons,

¹³⁶ Smart charging ability refers to technology typically found in smart phones that stops charging current flow to the battery when fully charged.

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casings, gaskets, seals, internal charging circuitry components, etc.) should be developed. It simply does not make sense to require component part manufacturers to submit PMTAs for each of their thousands of products. Instead, if a component part meets the applicable standard and is manufactured in accordance with GMP, it should be allowed to market.

- Standards should be developed to ensure consistent aerosol delivery. Boost circuits may be required to ensure consistent aerosol output by maintaining the heat level, or adjustable airflow features (*e.g.*, airflow sensors).
- Guidelines should be developed for the safe handling of nicotine when mixing e-liquids in the home.
- Of course, in addition to product standards, industry-specific GMPs should be developed to ensure that the devices and components are safely manufactured.

Once the standards (and GMPs) have been established, in order to most efficiently utilize both industry and FDA resources, e-cigarette and e-liquid manufacturing companies should be able to self-determine whether their products are compliant with all applicable standards and manufactured pursuant to GMPs subject, of course, to FDA verification and inspection. This is critical, as the Agency's ability to achieve the public health goals of the legislation will depend largely on whether it can efficiently utilize its resources.

2. Good Manufacturing Practices for E-Liquids

Good Manufacturing Practices or "GMPs" are systems and procedures that are designed to ensure the quality and safe manufacturing of a product. FDA has established GMPs codified in its regulations for food, dietary supplements, drugs and medical devices. With respect to tobacco products, the Tobacco Control Act gives FDA the authority to issue regulations related to tobacco product manufacturing practice in order to protect the public health and to assure that tobacco products are in compliance with the law. Specifically, Section 906(e) of the Act requires that FDA prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, preproduction design validation (including a process to assess the performance of a tobacco product), packing, and storage of tobacco products conform to (i) current GMPs or (ii) hazard analysis and critical control point methodology. Of importance, Section 906(e) also states that the GMP regulations "may differ based on the type of tobacco product involved."

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FDA should establish GMPs for the manufacture of e-liquids based on AEMSA's well-established e-liquid manufacturing standards, which are available online (at <http://www.aemsa.org/standards/>) and included in **Appendix I** hereto.¹³⁷ This is especially critical because many e-liquids used in cigalike devices are produced in China, where there is little regulatory oversight over their manufacture. AEMSA members have been able to demonstrate for several years now that content and quality in e-liquids (including nicotine content) is verifiable and sustainable.

As noted above, AEMSA is the first and only manufacturers' trade association completely dedicated to creating responsible and sustainable standards for the manufacturing of e-liquids. One of AEMSA's primary goals is to provide consumers with higher degrees of confidence that our members' products are manufactured with professionalism, accuracy and in a safe manner until such time as FDA promulgates GMPs for e-liquids. AEMSA believes that e-liquid manufacturers have the responsibility to:

- Verify the accuracy of nicotine content in e-liquid products;
- Ensure the quality of all ingredients in e-liquid products;
- Prepare e-liquid products in a clean, sanitary and safe environment;
- Ensure e-liquid products are packaged and delivered in a safe manner; and
- Provide a level of transparency into the monitoring and verification process.

These are the core beliefs underlying AEMSA's manufacturing standards. To assure that the public health is protected and that e-liquids are manufactured in compliance with the Tobacco Control Act, FDA should adopt GMPs based on these standards, which will ensure that e-liquids are not contaminated or manufactured in such a way that will result in the products being adulterated or misbranded.

¹³⁷ AEMSA has recently added Dr. Richard Soltero of InstantGMP, Inc. as a Subject Matter Expert (SME). InstantGMP, Inc. was founded in 2004 to develop web-based software for manufacturing products that must comply with current Good Manufacturing Practices (cGMP) and FDA requirements with the goal of making GMP production easy. Their software systems were developed to meet the standards of cGMP, GAMP and 21 CFR Part 11. InstantGMP has already been working with E-Liquid manufacturers and they now have a designated focus in this industry. They have a website section identified as "InstantGMP Vape" with sub categories for E-Liquid Manufacturing Software, E-Liquid calculator, E-Liquid SOPs, E-Liquid manufacturing process, FDA regulations timeline and a Vape glossary. See <http://www.aemsa.org/aemsa-welcomes-new-gmp-sme/>.

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b. Regulatory Framework No. 2: Neither Advanced Refillable Personal Vaporizers Nor Their Component Parts Should Not Be Considered “Covered Tobacco Products” Under the Deeming Regulation

Although the media often portrays e-cigarettes as heterogeneous, these products vary vastly in their function, content and appearance. As noted above, there is a clear distinction between cigalike devices and ARPVs, both in terms of the products themselves and who uses them. With these distinctions in mind, even if we assume, *arguendo*, that “electronic cigarettes” should be regulated under the same regulatory regime as combustible tobacco cigarettes, such regime should only apply to cigalike devices, and *not* to ARPVs and the refillable e-liquids used in them. Those products should instead be exempted from the meaning of “covered tobacco products,” along with premium cigars, under the NPRM’s “Option 2”.¹³⁸

ARPVs differ from cigalike devices in many of the same ways that premium cigars differ from cigarettes and little cigars. For example, both products are used by adult connoisseurs and can generally be found in specialty stores (cigar shops and tobacconists for premium cigars and “vape shops” for ARPV mods and e-liquids). These products are also much more expensive than their cheaper counterparts. ARPVs can cost a few hundred dollars to assemble, significantly more than the typical ready-made cigalike device which, like cigarettes and little cigars, which are widely distributed in locations where children might view them. Compared to cigalike models, ARPVs are not only better designed and incorporate numerous safety features described above, but also provide a greater potential public health benefit because they are able to more consistently deliver the nicotine-containing aerosol and because they may be used with a variety

¹³⁸ The NPRM proposes two alternatives regarding the scope of the rule: Option 1 would include all cigars as products covered by the proposed regulations and Option 2 would carve out an exception from coverage for “premium cigars.” A “premium cigar” would be defined as a cigar that: (1) Is wrapped in whole tobacco leaf; (2) contains a 100 percent leaf tobacco binder; (3) contains primarily long filler tobacco; (4) is made by combining manually the wrapper, filler, and binder; (5) has no filter, tip, or non-tobacco mouthpiece and is capped by hand; (6) has a retail price (after any discounts or coupons) of no less than \$10 per cigar (adjusted, as necessary, every 2 years effective July 1st, to account for any increases in the price of tobacco products since the last price adjustment); (7) does not have a characterizing flavor other than tobacco; and (8) weighs more than 6 pounds per 1000 units.

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of available refillable e-liquid flavors, which help smokers disassociate their habit with the taste of tobacco/combustion.¹³⁹

For these reasons, to the extent that access to inhalable nicotine from non-combusted sources *may* entice some non-smokers to start vaping and possibly to smoking, the likely culprit will be cigalike devices rather than ARPVs. As numerous studies and surveys have shown (several of which are described in Section IV), the vast majority of ARPV users are former smokers who, when they were unsatisfied with cigalikes, transitioned to the more advanced products instead of reverting back to combustible cigarettes. ARPV users also do not typically engage in “dual use” with cigarettes, because the advanced products are better able to satisfy their cravings.¹⁴⁰ Of course, any hypothetical “gateway” threat posed by cigalike devices must be balanced against the public health benefit those products offer by providing a less harmful alternative for cigarette smokers.

It is also important to highlight again that there is nothing to indicate that Congress intended to even regulate non-tobacco leaf products like e-cigarettes and ARPVs. As noted above, in a recent draft report by the House Appropriations Committee on the FDA funding bill, the Committee noted that exempting premium cigars from the scope of the Deeming Regulation made sense because there was “little mention of cigars” in the legislation.¹⁴¹ Specifically, the Committee stated that it believes that exempting premium cigars from regulation could be a viable solution, given that the Tobacco Control Act makes little mention of cigars throughout the legislation, and there is even less evidence that Congress intended to focus on the unique subset of premium cigars which “are shown to be distinct from other tobacco products in their effects on youth initiation, the frequency of their use by youth and young adults, and other such behavioral and economic factors.”

While there may be “little mention” of cigars in the Tobacco Control Act, there is no mention at all of e-cigarettes or e-liquids in either the text of the legislation or in the Congressional record. If FDA felt compelled to exercise its discretion to *not* deem premium cigars as covered tobacco products in its proposed “Option 2” of the NPRM then, for the reasons

¹³⁹ See Farsalinos, *et al.*, *Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices*, Scientific Reports 4, Article number: 4133, available online at: <http://www.nature.com/srep/2014/140226/srep04133/full/srep04133.html>.

¹⁴⁰ See McLaren, Neil, *Vaping.com Big Survey 2014 - Initial Findings General*, (2014), available <http://vaping.com/data/vaping-survey-2014-initial-findings>.

¹⁴¹ See <http://appropriations.house.gov/uploadedfiles/hrpt-113-hr-fy2015-agriculture.pdf>.

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noted above, it should do the same with respect to ARPVs, even if cigalike devices are eventually included.

Finally, even if ARPVs are deemed to be regulated tobacco products, it is critical that FDA not also consider the many component parts of such products to be covered tobacco products. While we understand that the tobacco product definition in Section 201(rr) of the Act includes any “component, part or accessory of a tobacco product,” subjecting the numerous component parts to the Tobacco Control Act requirements, in particular the premarket requirements, simply does not make sense. We note that with respect to the currently regulated tobacco products (*e.g.*, cigarettes, cigarette tobacco, smokeless tobacco and roll-your-own tobacco) FDA has chosen not to require component part manufacturers (*e.g.*, cigarette filter makers) to submit premarket applications for their products. In FDA’s Guidance for Industry on Section 905(j) Substantial Equivalence Reports, the Agency states that it intends to limit its enforcement of the Section 910 and 905(j) premarket requirements to *finished*, regulated tobacco products.¹⁴² Although the term “tobacco product” necessarily includes component parts such as cigarette rolling papers, filters or filter tubes, in order avoid the submission of duplicative information, FDA states that it does not intend to enforce the premarket application requirements for *components* of regulated tobacco products that are sold or distributed solely for further manufacturing into the finished products. Rather, FDA expects to receive all relevant information regarding tobacco products made with new or modified components in the premarket applications submitted by the end tobacco product manufacturers (*i.e.*, the cigarette manufacturer) in support of the finished tobacco products. This also means that it is up to the finished tobacco product manufacturers to ensure that accurate information about any new or modified components are included in the premarket applications for their products.¹⁴³

¹⁴² See *Guidance for Industry and FDA Staff: Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products* (Jan. 5, 2011), available online at: <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM239021.pdf>.

¹⁴³ The Guidance document states, in pertinent part, “[t]he [finished product] manufacturer must obtain appropriate market authorization for any changes to a tobacco product, including modifications to components. For example, if a finished cigarette manufacturer’s filter supplier changed the conformation of its filters, or changed the ingredients in its filters, the finished cigarette manufacturer would be responsible for including this change as part of its submission of its new product application.” See Section IV(A) of the Guidance.

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As noted above, there are dozens of separate parts that go into making the final ARPV, such as atomizers, cartomizers, clearomizers, batteries, chargers, tanks, endcaps, tubing, internal microprocessors/control circuits, springs, o-rings, drip-tips/mouth pieces, wicking materials, and other device components such as internal connectors, buttons, casings, gaskets, seals, and internal charging circuitry components. Further complicating any potential regulation of these components as tobacco products is the fact that these can all be used in devices in conjunction with zero-nicotine e-liquid; thus, in those situations, these products/components would not fall within FDA's tobacco product authority. Additionally, many of these parts and materials used to make them are used in other consumer goods, such as cell phones, laptop computers, toys, remote controls, power stations and cameras.

To require e-cigarette and ARPV component part manufacturers to submit PMTAs for each of their hundreds of products, would result in an effective ban of these products. FDA should develop product standards/specifications for each component type, as well as standards for what combinations of components may be used together. If a component part meets the applicable standard and is manufactured in accordance with GMP, it should be allowed to market. Furthermore, as discussed in Regulatory Framework No. 3 below, component part manufacturers should be able to submit to FDA the confidential manufacturing, composition and other proprietary business information about their products in a confidential Tobacco Product Master File for authorized customers (*i.e.*, ARPV manufacturers) to reference in their FDA submissions, as necessary.

c. Regulatory Framework No. 3: FDA Should Establish a New “Grandfather Date” to Apply to E-cigarette and E-liquid Products and Model the Substantial Equivalence Requirements Based on the 510(k) Pathway for Medical Devices

The Tobacco Control Act requires tobacco manufacturers and importers to obtain FDA premarket review prior to introducing “new” tobacco products into interstate commerce. A new tobacco product is defined as “(1) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or (2) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.”¹⁴⁴ In other words, the premarket review

¹⁴⁴ 21 U.S.C. § 387j(a)(1)(A)-(B).

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requirement applies to all tobacco products first introduced to the market or modified in any way after the February 15, 2007 “Grandfather Date”.¹⁴⁵

The NPRM for the Deeming Regulation imposes the existing February 15, 2007 Grandfather Date to newly covered tobacco products. Thus, if the proposal were to become effective as drafted, any deemed tobacco product, including e-cigarettes and their e-liquid components, would be considered “new tobacco products” subject to premarket review if they were not commercially marketed in the United States as of February 15, 2007 or modified in any way from a product that was commercially marketed after that date. FDA states in the NPRM that because the Grandfather Date is set by the statute, it does not believe it has the authority to change it by regulation. Of course, as detailed in Section IV above, there is much precedent supporting that FDA can use its rulemaking authority to find regulatory solutions other than those explicitly anticipated by Congress and set forth in the statute.

AEMSA is not aware of any e-cigarette or e-liquid product that was commercially marketed on February 15, 2007. Because there are no viable predicate products that were on the market on that date, no e-cigarettes or e-liquids products would be considered grandfathered. Recognizing the difficulty that imposing the statutory Grandfather Date will cause the industry, FDA has proposed a compliance policy in the NPRM that would delay enforcement of the premarket authorization requirements for the newly deemed products. Under this policy, FDA would allow any e-cigarette or e-liquid product marketed after February 15, 2007 through two years after the effective date of the Deeming Regulation to remain on the market provided (1) either a PMTA (or SE Report¹⁴⁶) for such product is submitted by the two year anniversary of the effective date of the regulation, and (2) until such time as FDA denies the premarket submission. This means that if the NPRM becomes effective as drafted, all e-cigarette and e-liquid products marketed between now and through two years after the effective date of the Deeming Regulation will need to go through the PMTA process to remain on the market. For products *not* on the market at the end of the two year compliance period, e-cigarette and e-liquid manufacturing companies will need to *first* obtain PMTA authorization from the Agency before introducing such products into commerce.

¹⁴⁵ Premarket review means that before introducing a new tobacco product to the market, the manufacturer/importer must obtain from FDA either (1) an order authorizing its marketing after review of a PMTA submission, (2) a finding of “substantial equivalence” to a pre-February 15, 2007 tobacco product (or another product previously deemed substantially equivalent), or a (3) “minor modification” exemption from the substantial equivalence requirements.

¹⁴⁶ But because there are no grandfathered e-cigarette or e-liquid products, the PMTA is the only viable premarket pathway.

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This two year post-effective date compliance period buffer, however, does nothing but delay the complete collapse of the e-cigarette and e-liquid industries as they exist today. As discussed in Section IV above, requiring all e-cigarette and e-liquid products to obtain premarket authorization by way of a PMTA will result in these products eventually being removed from the market and effectively banned, even though this was never intended by Congress. While such a result would undoubtedly be disastrous for the public health, as millions of former smokers would likely turn back to harmful tobacco-leaf and combusted products, it may be prevented if the Agency utilizes a more appropriate grandfather date for these novel, significantly less risky products.

i. FDA Should Establish a New “Grandfather Date” to Apply to E-cigarette and E-liquid Products

FDA should use its rulemaking authority to establish a more appropriate grandfather date to specifically apply to e-cigarettes and e-liquids other than the February 15, 2007 date provided in the statute, which was only intended to apply to tobacco-leaf containing products. As detailed in Section IV herein, there are numerous reasons why it simply does not make sense to apply the February 15, 2007 date to e-cigarettes and their components; namely, Congress did not intend the Tobacco Control Act requirements, such as the statutory Grandfather Date, to be strictly applied to novel products that do not contain tobacco leaf and only deliver aerosolized nicotine. In this regard, the underlying purpose for establishing the Grandfather Date was to create a rigorous premarket process to ensure that new, more harmful *tobacco leaf-containing* products did not enter the market. But as detailed above, e-cigarettes and their e-liquid components are drastically less harmful than tobacco leaf products and, in particular, combusted products. These products provide a clear public health benefit, and the rapidly evolving technology is only making these products safer and less risky. Innovation in the e-cigarette industry is much different from that of traditional tobacco. As companies have become more sophisticated, the uses of higher quality ingredients and parts, as well as production quality standards have become more common. There is a vibrant competition among e-cigarette and e-liquid manufacturers to develop safer products for adult smokers looking to transition to less harmful forms of nicotine.¹⁴⁷

¹⁴⁷ A few examples of the types of safety and engineering advancements that have now become common in e-cigarettes (particularly ARPVs) include improved battery and charger technology, auto-shut off capabilities, short-circuit protections, temperature limitations, and e-liquid wicking and quality improvements. E-liquids are also much less harmful (*i.e.*, contain fewer unintended impurities, etc.) as the quality of ingredients and manufacturing processes have improved.

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Additionally, e-cigarettes were actually prohibited by FDA from entering the U.S. market back in 2007. At that time, FDA considered e-cigarettes to be unapproved drug delivery devices. In 2008, the Agency seized shipments of some e-cigarette products that were being imported from China because it viewed them as unapproved drug delivery devices. It was only after the decision in *Sottera* that the Agency was forced to recognize that e-cigarettes are not drugs/drug delivery devices but can be allowed on the market as unregulated tobacco products. Thus, it makes no sense to apply the February 15, 2007 Grandfather Date to products that, in FDA's view, were not even allowed to be on the market at that time.

Even if there was a viable predicate e-cigarette on the market on the statutory Grandfather Date, such product would most likely be a rudimentary, disposable cigalike device. Electronic cigarette technology has improved immensely since those first products entered the U.S. A few examples of the types of safety and engineering advancements that have now become common in e-cigarettes (particularly ARPVs) include improved battery and charger technology, auto-shut off capabilities, short-circuit protections, temperature limitations, and e-liquid wicking and quality improvements. E-liquids are also much less harmful today (*i.e.*, contain fewer unintended impurities, etc.) as the quality of ingredients and manufacturing processes have improved. Applying the statutory Grandfather Date to this industry would allow manufacturers to produce products identical to those that may have been on the market on that date, and to ignore and exclude technological advancements that benefit the public health.¹⁴⁸ In short, applying the 2007 Grandfather Date would completely disincentivize any and all current and future innovations, as well as eliminate many that have already been adopted and that are in development. For these reasons, it makes little sense for FDA to strictly apply the original Grandfather Date to e-cigarettes.

Instead, FDA should use its enforcement discretion to allow e-cigarettes and their e-liquid components that are on the market on the effective date of the Deeming Regulation to be grandfathered and, therefore, remain on the market without obtaining FDA premarket authorization.¹⁴⁹ To understand why this date makes the most sense, it is important to consider the why February 15, 2007 was selected as the statutory Grandfather Date. That date has no

¹⁴⁸ As discussed below, because the “different questions of public health” legal standard for substantial equivalence requires assessing the population-level impact of any product modifications, it would be very difficult and potentially impossible to demonstrate that new safety features and engineering advancements do *not* raise different questions of public health and so are substantially equivalent to a grandfathered product.

¹⁴⁹ Such grandfathered products, of course, will be able to serve as predicate products for SE Reports for future products.

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special meaning, other than it was simply the date that the House and Senate bills that eventually became the Tobacco Control Act were reintroduced in Congress, after previous versions of the bill had failed to pass.¹⁵⁰ In fact, even though it was H.R. 1256, introduced on March 3, 2009 in the 111th Congress,¹⁵¹ that was ultimately signed by the President, we suspect that the original February 15, 2007 grandfather date was kept in the legislation, at least in part, because that was the date that put the tobacco industry on official notice not only that it would be subject to FDA's authority, but *how* it would be regulated.

Using this same logic of “first notice,” FDA should establish the effective date of the final Deeming Regulation as the grandfather date for e-cigarettes and e-liquids. This is especially true if the Agency proposes a new regulatory scheme tailored for these products in the final rule, as these comments advocate. The grandfather date should be delayed concurrent with implementation of an appropriate regulatory scheme appropriate for the risk involved. As noted in Section II above, the Agency failed to promulgate an *advanced* notice of proposed rulemaking, even though the NPRM requests the public to propose alternative regulatory frameworks for e-cigarettes. In light of these requests, the Agency should expect to receive many comments about how to regulate e-cigarettes. It is entirely possible, and we certainly hope, that the Agency seriously considers such comments as it prepares its final rule. If FDA chooses to incorporate new requirements tailored to e-cigarettes in the final rule, it should make the effective date of such regulation the new grandfather date for these products in order to provide the industry with enough time to prepare for regulation and to prevent its complete collapse.¹⁵²

¹⁵⁰ See *Statement of Rep. Henry A. Waxman Reintroduction of the “Family Smoking Prevention and Tobacco Control Act,”* dated February 15, 2007, available online at: <http://oversight-archive.waxman.house.gov/documents/20070216165108-78937.pdf>; see also Library of Congress Summary of S. 625 (110th): Family Smoking Prevention and Tobacco Control Act, available online at: <https://www.govtrack.us/congress/bills/110/s625#summary/libraryofcongress>.

¹⁵¹ See <https://www.govtrack.us/congress/bills/111/hr1256/text>.

¹⁵² Two other potential alternative grandfather dates for e-cigarettes and e-liquid products are April 25, 2014, the NPRM publication date, or April 25, 2011, the date the Agency published a letter to stakeholders on its website indicating that it intended to capture e-cigarettes as regulated products via its rulemaking authority. Neither of these dates, however, would grandfather the many now standard safety features in today's advanced e-cigarettes. This is a major concern because, as discussed below, demonstrating that such changes do not raise “different questions of public health” is incredibly difficult, as it requires assessing the population-level impact. Rather, FDA should use the effective date of the Deeming Regulation

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ii. FDA Should Model the Substantial Equivalence Requirements Based on the 510(k) Pathway for Medical Devices

In addition to establishing a more appropriate grandfather date for e-cigarettes and their e-liquid components, because of the significantly different risk profile of e-cigarettes compared to conventional cigarettes, the Agency should acknowledge that a less rigorous implementation of substantial equivalence documentation is appropriate. Specifically, FDA should implement the SE pathway for such products in a manner similar to the implementation of the medical device regulation under Section 510(k) of the FDCA, as the current substantial equivalence regulatory scheme is untenable for these new products.

Under the current framework, even the most minor changes to a predicate product trigger the premarket review requirement. FDA has issued a number of guidance documents confirming its interpretation that *any* modification to a grandfathered tobacco product converts that product to a “new tobacco product” subject to premarket review.¹⁵³ This means that either a full Substantial Equivalence (SE) Report¹⁵⁴ (or even more burdensome PMTA) must be submitted

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as the new grandfather date for these products to ensure that it captures the latest engineering and safety advancements that benefit the public health, and also model the SE pathway for e-cigarettes after the 510(k) pathway for medical devices, as discussed below.

¹⁵³ See Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products, dated January 2011, and Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions, dated September 2011.

¹⁵⁴ An SE Report for a tobacco product is a complex filing that requires demonstrating that a new product is either identical to a grandfathered product or that its different “characteristics” do not raise different questions of public health. “Characteristics” is defined in Section 910(a)(3)(B) of the Act as “the materials, ingredients, design, composition, heating source, or other features of a tobacco product.” FDA has recommended in their guidance documents that SE Reports include side-by-side quantitative and qualitative comparisons of the new and predicate products with respect to all product characteristics. This means that an SE Report must list all design features, ingredients, materials, levels of HPHCs and other features, and provide a description of product composition and, if applicable, heating source. FDA could also request manufacturers provide consumer perception data, clinical data, abuse liability data, and toxicology data to show that a new product with different characteristics does not present different questions of public health. See *Guidance for Industry and FDA Staff: Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products* (Jan. 5, 2011), available online at:

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virtually every time a manufacturer makes even the slightest change to the design, component, part, constituent, labeling or even packaging of a grandfathered tobacco product. Indeed, FDA has indicated that, with respect to tobacco leaf-containing products, it will enforce the premarket approval requirements for even the most minor changes, stating that if a “supplier of a component (*e.g.*, the filter) began using a new processing aid (*e.g.*, an antimicrobial agent) for a sub-component (*e.g.*, paper used for the filter’s plug wrap) and the change is so minor that it is not even capable of being quantified in the finished product,” such modified product still cannot be marketed without FDA premarket approval.¹⁵⁵ The result of FDA’s strict interpretation of the statute has been a flood of SE Reports by the tobacco industry that have completely crippled the Agency’s ability to respond in a timely manner. On October 21, 2013, the Government Accountability Office (GAO) released a report identifying significant shortcomings in FDA’s progress toward reviewing SE Reports submitted by the tobacco industry.¹⁵⁶ The GAO report noted that in the three years since FDA received the first SE Report in June 2010, the Agency made final decisions on only 17 of the 3,788 submissions received at the time of the report. On average, it took the Agency over 1 ½ years to complete just the initial review steps (*e.g.*, jurisdiction and completeness reviews) for Provisional SE Reports, and 6 months for Regular SE Reports it received.¹⁵⁷

(...continued)

<http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM239021.pdf>.

¹⁵⁵ See *Draft Guidance for Industry and FDA Staff – Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions* (September 9, 2011), available online at <http://www.fda.gov/downloads/TobaccoProducts/ResourcesforYou/ForIndustry/UCM271239.pdf>. We further note that FDA’s draft guidance *Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007* (April 22, 2011), available online at: <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM334750.pdf>, provides information on what evidence is needed to demonstrate that a product is indeed grandfathered.

¹⁵⁶ See Report GAO-13-723 from the U.S. Government Accountability Office, “New Tobacco Products: FDA Needs to Set Time Frames for Its Review Process,” available on the GAO’s website at: <http://www.gao.gov/products/GAO-13-723>.

¹⁵⁷ A Provisional SE Report is an SE Report filed with FDA by March 22, 2011 for a new tobacco product commercially marketed after February 15, 2007 but before March 22, 2011, pursuant to Section 905(j)(2) of the Tobacco Control Act. A Regular SE Report does not meet
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FDA's current approach to premarket review has not only placed a tremendous burden on FDA, but also on the industry itself. Requiring manufacturers to prepare complex SE Reports or PMTAs nearly every time they make a change to their product or its labeling or packaging will significantly drain resources and put most small companies out of business. Applying these requirements to the e-cigarette and e-liquid industries will only exacerbate the situation, as there are thousands of e-cigarette, e-cigarette component and e-liquid manufacturers that make tens and of thousands of products that are constantly being modified to improve safety and to adjust to changing consumer preferences. Even if the FDA uses a more appropriate grandfather date for these products, the industry will be forced to prepare, and the Agency will be inundated with, thousands of premarket applications. To avoid this unreasonable burden on both FDA and industry, the Agency should use its rulemaking authority to implement a regulatory solution: for deemed products that do not contain tobacco leaf, in addition to establishing a new grandfather date, the Agency should implement the Tobacco Control Act's substantial equivalence pathway in a manner similar to the 510(k) program established for devices.

Section 510(k) of the FDCA provides that a medical device manufacturer may only market a new or modified device if, after submitting a premarket notification to FDA, the Agency determines that the device is substantially equivalent to a legally marketed predicate device. FDA realized, however, that requiring premarket notification for every change made to a device was not an effective use of resources and, in yet another example of the Agency using its rulemaking authority to create a regulatory solution not explicitly anticipated by Congress, promulgated a final rule implementing the 510(k) program in which it concluded that it "should not require a premarket notification for every change...since too many...changes are made on a regular basis."¹⁵⁸ Accordingly, FDA exempted from the substantial equivalence filing requirement changes made to devices that had little or no impact on health, and established regulations providing that only changes that could "significantly affect the safety or effectiveness of the device," or that constitute a "major change or modification" in the device's intended use, require a 510(k) submission.¹⁵⁹ FDA has published guidance for industry to help manufacturers determine whether a 510(k) should be submitted for a particular type of change, and has even

(...continued)

the statutory criteria for a Provisional SE submission (*i.e.*, the subject tobacco product was either not on the market before March 22, 2011 or is not subject to a report filed by that date).

¹⁵⁸ See *Establishment Registration and Premarket Notification Procedures*, Final Rule, 42 Fed. Reg. 42,519, 42,522 (Aug. 23, 1977).

¹⁵⁹ See 21 C.F.R. § 807.81(a)(3).

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developed a flowchart that can be used by manufacturers when analyzing how changes to their devices may affect safety or effectiveness.¹⁶⁰ Although a device manufacture can determine for itself whether a product change merits submission of a 510(k) application, FDA retains the authority to inspect a manufacturer's documentation concluding that a filing was not required for a particular modification, and may initiate enforcement proceedings if it disagrees with the manufacturer's conclusion.

Because e-cigarettes and their components are so much more similar to medical devices than tobacco leaf-containing products, FDA should promulgate a similar regulatory framework governing the substantial equivalence pathway for these products, whereby premarket (*i.e.*, SE Report) authorization will only be required for significant changes that may be expected to raise different questions of public health. Moreover, manufacturers should be permitted to make the initial determination of whether an SE Report is required. Such an approach would be completely consistent with the Tobacco Control Act and would better allow FDA to achieve Congress's public health goals.

FDA has actually recognized that the 510(k) program may serve as a model for the substantial equivalence pathway for tobacco products. A recent *Food and Drug Policy Forum* published by the Food and Drug Law Institute addressed this very point¹⁶¹:

Thus, in the preamble to the final regulations for minor modification exemptions under FD&C Act Section 905(j)(3), the Agency noted that "FDA did consider the requirements applicable to medical devices when developing this rule, but concluded those requirements are inconsistent with Section 905(j)(3).... Section 905(j)(3) specifically requires FDA to make certain findings, including a determination of whether the modification would be a minor modification of a tobacco product that can be sold under the [Tobacco

¹⁶⁰ See *Deciding When to Submit a 510(k) for a Change to an Existing Device* (Jan. 10, 1997), available online at: <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080235.htm>.

¹⁶¹ See J. Benneville Haas and Natalie N. Sanders, *Substantial Equivalence Under the Family Smoking Prevention and Tobacco Control Act of 2009: How Can FDA Create a More Effective and Efficient Regulatory Scheme?*, FDLI Food and Drug Policy Forum, April 10, 2013, at 8-9.

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Control Act]....”¹⁶² Importantly, the Agency’s statements are limited to a discussion of the implementation of Section 905(j)(3); FDA did not comment on the plausibility of using the 510(k) Program as a model for the implementation of the substantial equivalence pathway under Section 905(j). Indeed, the very textual distinction upon which FDA based its conclusion about Section 905(j)(3) is not applicable to the statutory language that establishes the substantial equivalence pathway under the Tobacco Control Act. Indeed, Section 513(i) of the FD&C Act defines substantial equivalence in the context of medical devices, stating that substantial equivalence “means...that the Secretary by order has found that the device [has met the applicable standards].” This language is analogous to that found in Section 910 of the Tobacco Control Act, providing that substantial equivalence for tobacco products “means...that the Secretary by order has found that the tobacco product [has met the applicable standards].” **Thus both the statutory texts and FDA’s prior practice suggest that the 510(k) Program should serve as a model for implementing the substantial equivalence review under the Tobacco Control Act.**

(Emphasis added.) We further note that FDA has already exercised enforcement discretion to waive the substantial equivalence requirements for certain types of modifications made to tobacco products that are not expected to affect the public health profile of the product. Specifically, SE Reports do not need to be submitted for the following product modifications:

- Certain label and packaging changes as follows: (1) removal of the descriptors “light,” “mild,” or “low” in compliance with the Act, (2) inclusion of any required graphic warnings, (3) package type modifications (*i.e.*, hard to soft pack or vice versa), provided such change did not modify the tobacco product in any other way (*e.g.*, a change in moisture content, shelf life, ingredient composition, nicotine delivery, harmful/potentially harmful constituents), and (4) changes made to font size, ink color, or background color of the packaging or labels.¹⁶³

¹⁶² See 76 Fed. Reg. 38,961, 38,963 (July 5, 2011), available at <http://www.gpo.gov/fdsys/pkg/FR-2011-07-05/pdf/2011-16766.pdf>.

¹⁶³ See *FDA Draft Guidance for Industry and FDA Staff: Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions*, 76 Fed. Reg. 55,927 (September 9, 2011), available at: <http://www.fda.gov/downloads/TobaccoProducts/ResourcesforYou/ForIndustry/UCM271239.pdf>.

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- When a new supplier is used for the same additive with identical specifications;¹⁶⁴ and
- Tobacco blending changes required to address the natural variation of tobacco in order to maintain a consistent product.¹⁶⁵

Moreover, just as device manufacturers are allowed to determine whether changes made to their products need 510(k) approval, tobacco product manufacturers are permitted to self-determine whether one of the above SE Report exceptions apply. FDA has also exercised similar discretion in not fully enforcing other provisions of the Tobacco Control Act. For example, even though Section 904(a)(3) requires tobacco product manufacturers to report the amount of HPHCs found in their products, FDA published guidance stating that it would, for now, only require the submission of data on only 20 of the 93 substances that the Agency has identified as HPHCs. FDA justified this decision as being both expedient and practical.¹⁶⁶ Because FDA's ability to achieve the public health goals of the legislation will largely depend on its ability to efficiently utilize resources, the Agency should, for the same reasons, exercise its discretion and implement a substantial equivalence framework for e-cigarettes and e-liquids similar to the 510(k) program for medical devices.

d. Regulatory Framework No. 4: FDA Should Use its Establish an Alternative Framework for E-Liquid Manufacturing Companies to Comply with Section 904(a)(1) Ingredient Listing Requirement

Section 904(a)(1) of the Tobacco Control Act requires each tobacco product manufacturer or importer to submit a listing of all ingredients, including tobacco, substances, compounds and additives, that are added by the manufacturer to the tobacco product "by brand and by quantity in each brand and subbrand." With respect to the refillable e-liquid industry, this means that each producer will need to submit a separate list of ingredients for *each* of its unique product formulations. Even the smallest e-liquid producers often have dozens of unique products (with individual stock keeping units (SKUs)), while the largest companies produce hundreds or even thousands of unique formulations. Products vary by flavor combinations, and PG/VG and

¹⁶⁴ *Id.* at 6.

¹⁶⁵ *Id.* at 8.

¹⁶⁶ See *FDA Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the FDCA*, 77 Fed. Reg. 20030 at 3 (April 3, 2012), available online at: <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297828.pdf>.

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nicotine concentrations. As discussed above, there is likely somewhere between 5,000 and 15,000 individual manufacturers and retailers producing e-liquid products in the U.S., nearly all of which are small businesses (*i.e.*, less than 350 employees), including vape shops that mix their own products. If we conservatively assume that there are only 5,000 e-liquid producers in the country and that each such company has only 20 unique e-liquid formulations, that means that there are *at least* 100,000 unique e-liquid products on the market.

First, FDA has greatly underestimated the total number of e-liquid products that are on the market in the NPRM, estimating that only 188 companies in the “other tobacco, e-cigarettes, and nicotine product manufacturers” category will submit 8.9 ingredient lists each, for a total of 1,675 annual responses. This is only a fraction of the number of ingredient list FDA should expect to receive. Second, the collection of such information in this manner and format (*i.e.*, separate ingredient listings for each unique e-liquid formulation) would be prohibitively expensive for the majority of the thousands of small e-liquid manufacturers in the country (each of whom have anywhere from dozens to hundreds of unique product formulations), and is not necessary for the proper performance of FDA’s function. This vast amount of information would not only be very difficult and expensive for the many small e-liquid manufacturing companies to produce for FDA, but would also inundate the Agency with superfluous information that would only slow down the regulatory process. While we understand that information on what products are on the market and what ingredients are being consumed is important for FDA to have, the Agency should use its enforcement discretion to obtain this data in a less burdensome, more practical manner.

Specifically, FDA should use its enforcement discretion to implement an alternative framework for e-liquid manufacturing companies to comply with Section 904(a)(1), whereby each company would only be required to submit a *single* table of all the ingredients used in all of its e-liquid products, along with the use-level (concentration) ranges (*i.e.*, minimum and maximum percentages) of each of those ingredients in the products that are made with those ingredients. A hypothetical example of such a table is as follows:

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Ingredient Listing for ACME E-Liquid, Inc. (Hypothetical)			
Ingredient	Chemical Abstract Services Registry Number (CAS Reg. No.)	Minimum Use-Level in Products that Contain Ingredient (%)	Maximum Use-Level in Products that Contain Ingredient (%)
Nicotine	54-11-5	0.1	2.4
Propylene Glycol	57-55-6	35	97
Glycerin	56-81-5	35	97
Distilled Water	7732-18-5	.1	2
Ethyl maltol (2-ethyl-3-hydroxy-4-pyrone)	4940-11-8	.001	0.2
2-Cyclopenten-1-one	80-71-7 or 930-30-3	.001	1
Benzaldehyde, 3,4-dimethoxy-	120-14-9	.008	0.5
Acetic Acid	64-19-7	.001	0.3
Furfural	98-01-1	.002	1
Ethyl alcohol	64-17-5	.002	0.2
Iso-amyl acetate (1-butanol, 3-methyl-, acetate)	123-92-2	.002	0.1
Ethyl acetate	141-78-6	.001	0.3
Iso-amyl alcohol	123-51-3 or 584-02-1	.001	0.5

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Ingredient Listing for ACME E-Liquid, Inc. (Hypothetical)			
Ingredient	Chemical Abstract Services Registry Number (CAS Reg. No.)	Minimum Use-Level in Products that Contain Ingredient (%)	Maximum Use-Level in Products that Contain Ingredient (%)
Acetaldehyde	75-07-0	.001	0.2
Ethyl butyrate	105-54-4	.001	0.3
Benzaldehyde	100-52-7	.005	0.1
Ethyl propionate (propanoic acid, 3- methyl-, acetate)	105-37-3	.001	0.4

Furthermore, under this alternative framework, e-liquid manufacturing companies should be allowed to amend their ingredient list if they added or removed ingredients or increased the maximum concentration of any of their current ingredients in any of their products, rather than submit a *new* ingredient list specific to the new product. Such a framework would provide FDA with all the information it needs for the proper performance of its function (*i.e.*, information on what substances are being used and at what levels), while dramatically reducing the cost and administrative burden for both e-liquid manufacturing companies, as well as FDA by decreasing the overall number Section 904(a)(1) submissions. Again, because FDA's ability to achieve the public health goals of the legislation will largely depend on its ability to efficiently utilize resources, the Agency should exercise its discretion and implement this alternative framework for the Section 904(a)(1) ingredient listing and disclosure requirement for e-liquids.

i. FDA Should Establish a Master File System for Suppliers and Component Manufacturers to Disclose Confidential Information

As discussed above, one of the primary reasons why ARPVs provide a public health benefit is because they may be used with refillable e-liquids that come in a multitude of flavors. These flavors help smokers dissociate their habit with the taste of tobacco and combustion. There are thousands of e-liquid manufacturers and vape shops across the country which produce tens of thousands of individual e-liquid products. These e-liquid manufacturing companies

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purchase their formulated flavor ingredients from flavor house suppliers. Of course, these flavor houses consider their formulations to be highly confidential proprietary business information and do not disclose them to their e-liquid producing customers. Thus, a major concern is that because few flavor suppliers may be willing to disclose confidential commercial information and trade secrets to their customers, most e-liquid producers will *not* be able to meet their ingredient disclosure obligations under Section 904(a)(1). This will also make it prohibitively difficult to obtain premarket authorization for changes/adjustments made to flavor and e-liquid formulations in the normal course of business (e-liquid manufacturing companies will have to obtain the confidential information from their suppliers far enough in advance to timely prepare and submit a Section 905(j) SE Report, for example).

To address this situation, FDA should establish a “Tobacco Product Master File” (TPMF) system similar to the Agency’s Drug Master File (DMF) and Food Additive Master File (FAMF) systems to allow for e-cigarette and e-liquid suppliers to submit to FDA their confidential product information (including information on formulations, facilities, processes, and articles used in the manufacturing, processing, packaging, and storing of ingredients used in e-liquids).¹⁶⁷ The information contained in the TPMF may be used to support FDA submissions, including Section 904(a)(1) ingredient disclosures and premarket applications. A flavor house could submit a TPMF for each of its confidential flavor formulations and indicate which of its e-liquid customers are authorized to reference that TPMF in its FDA filings. Thus, to provide a hypothetical example, if ABC Flavor House submits a TPMF, which is subsequently designated as TPMF No. 001, for its “Flavor Formulation X” and indicates therein that ACME E-Liquid, Inc. is one of its authorized customers, then AMCE E-Liquid would simply indicate in its Section 904(a)(1) ingredient list that it uses Flavor Formulation X, which is the subject of TPMF No. 001. This would provide FDA with all of the information it needs, while preserving its confidential nature.

* * *

¹⁶⁷ See FDA’s *Drug Master File Guidelines*, available online at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm>.

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AEMSA appreciates the opportunity to submit these comments to the NPRM for the Deeming Regulation as well as FDA's continuing effort to seek input from stakeholders. For the reasons set forth above, we believe that FDA has the legal authority to regulate e-cigarettes, including advanced refillable personal vaporizers and their e-liquid components, differently than tobacco leaf-containing product. The Agency should use the enforcement discretion envisioned by Congress and permitted by the statute to establish regulatory requirements tailored to the product types it chooses to deem as regulated products, including products that only deliver aerosolized nicotine. We recommend implementing the regulatory frameworks for e-cigarettes and e-liquids described in these comments. AEMSA would be more than willing to meet with the Agency to discuss these comments at its earliest convenience.

Respectfully submitted,



Lou Ritter
President and Consumer Advocate,
American E-Liquid Manufacturing Standards Association

On behalf of:

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- | | |
|---|--|
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| 3. Firebrand – Brian Gage | 16. OKC Vapes - Stephanie Durst |
| 4. Hot Vapes – Tim Roche | 17. Purebacco – Kevin Beilman |
| 5. iVape/JP Ventures LLC – Joe Battista | 18. Tampa Vapor – John Synychak |
| 6. J Vapes – Jourdan Wheeler | 19. Texas Select Vapor – Brett Coppolo |
| 7. Juicy Vapor – Anthony Brancato | 20. The Vapor Bar – Schell Hammel |
| 8. Kalamazoo Vapor Shop – James Bearup | 21. The Vaper's Knoll – Richard Gue |
| 9. Madvapes – Scott Church | 22. Two Peas in a Pod – Orlan Johnson |
| 10. Mid Cities Vapor – Steven Belcher | 23. VaporHQ – Adam Black |
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Enclosure: Appendix I – AEMSA E- Liquid Manufacturing Standards

Appendix I

AEMSA E-Liquid Manufacturing Standards

2014 E-Liquid Manufacturing Standards



Creating responsible and sustainable practices and process
for the safe manufacturing of “e-liquids” used in electronic
cigarettes

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Version 2.0

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Purpose

The purpose of these Standards is to create a responsible and sustainable practices and process for the safe manufacturing of “e-liquids” used in electronic cigarettes. Our members believe we have a responsibility to self-regulate the e-liquid manufacturing process based on professional criteria. AEMSA aims to accomplish this by creating, implementing and upholding standards for the manufacture of e-liquids. One of AEMSA’s primary goals is to provide consumers with higher degrees of confidence our members’ products are manufactured with professionalism, accuracy and safety

AEMSA standards are established based on the following Core Beliefs:

- We have a responsibility to verify the accuracy of any nicotine content in the products we distribute.
- We have a responsibility to ensure the quality and safety of all ingredients in our e-liquids.
- We have a responsibility to prepare our products in a clean, sanitary and safe environment.
- We have a responsibility to ensure our products are packaged and delivered in a safe manner.
- We have a responsibility to provide a level of transparency into the monitoring and verification process.

The 2012 AEMSA Standards are living documents and subject to changes according to the AEMSA corporate structure and procedures

Scope

These standards apply to all AEMSA general members that engage in the manufacturing or processing of E-liquids. 2012 E-Liquid Manufacturing Standard will be used as a basis for:

- Evaluating compliance for membership acceptance
- Confirming compliance of existing membership

Definitions

Term	Definition
Active Age Verification	Taking active measures to ensure that all customers are of legal age. Can be accomplished in many ways including Photo Identification and 3rd party verification systems. Note: Having pop up box asking the person to indicate they are over a specified age is not Active Age Verification

ASTM - American Society for Testing and Materials	An international standards organization that develops and publishes voluntary consensus technical standards for a wide range of materials, products, systems, and services
Chain of custody	The chronological documentation or, showing the custody, control, transfer, analysis, and disposition of physical component; tracking a product along the supply chain to the point of sale
Components	A part or element of a larger whole; a substance that forms part of a mixture. Any substance, material or the tangible substance that goes into the manufacturing of e-liquid
Contaminants	An impurity or foreign substance present in a material or environment that affects one or more properties of the material
Custard Notes	Flavor compounds that impart a buttery, creamy, or custard taste or sensation. Most commonly used are acetoin, acetyl propionate and diacetyl
Dedicated Manufacturing Space	A clean safe environment that is used exclusively for the manufacturing of e-liquid
Diacetyl	A natural byproduct of fermentation. It is a vicinal diketone (two C=O groups, side-by-side) with the molecular formula C ₄ H ₆ O ₂ . Diacetyl occurs naturally in alcoholic beverages and is added to some foods to impart a buttery flavor. It has been eliminated from many commercial flavorings due to risk of lung damage
Direct Operation	A facility or process where Full time employees for an organization directly supervise and oversee production and process
DIY	Do it Yourself
Electronic cigarette	Also known as an e-cigarette (e-cig) is an electrical inhaler that vaporizes a propylene glycol and/or glycerin-based liquid solution into an aerosol mist simulating the act of tobacco smoking
E-liquid	Liquid for producing vapor in electronic cigarettes, known as e-juice or e-liquid
E-liquid manufacturing	Fabrication: the act of making something (a product) from raw materials; to include all processes from supply acceptance to the point of customer delivery
Free-base	An amine or nitrogen-containing organic compound, such as nicotine, in its basic (high pH) form, in contrast to its acidic (low pH) form, which is often called the "salt" form. Unless an acid has been added to nicotine, or it is purchased as the salt, it is in the free-base form. Free-base describes the form of the compound, not its purity
Generally Recognized as Safe (GRaS)	Generally recognized as safe (GRAS) is an American Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts, and so is exempted from the usual Federal Food, Drug, and Cosmetic Act (FFDCA) food additive tolerance requirements
Indirect Operation	A facility or process where supervision and/or oversight of production and/or process for an organization is conducted by a 3rd party or contractor (subcontractor)
Mg / ml	Milligrams per Milliliter – a scale (or ratio) for measuring an ingredient component, in liquid form, where accuracy is measured in mg per ml - or a percentage equivalent

Nicotine	Nicotine is an alkaloid found in the nightshade family of plants (Solanaceae) that acts as a nicotinic acetylcholine agonist. The biosynthesis takes place in the roots and accumulation occurs in the leaves of the Solanaceae. It constitutes approximately 0.6–3.0% of the dry weight of tobacco and is present in the range of 2–7 µg/kg of various edible plants
NIST -The National Institute of Standards and Technology	A non-regulatory agency of the United States Department of Commerce. The institute's official mission is to: Promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life
OSHA	The United States Occupational Safety and Health Administration (OSHA) is an agency of the United States Department of Labor. Congress established the agency under the Occupational Safety and Health Act, was signed into law on December 29, 1970. OSHA's mission is to "assure safe and healthful working conditions for working men and women by setting and enforcing standards and by providing training, outreach, education and assistance"[2]. The agency is also charged with enforcing a variety of whistleblower statutes and regulations
PPM	Parts Per Million
SINGLE-USE ARTICLES	Utensils, containers and tools designed and constructed to be used once and discarded
Tamper Evident	Tamper-evident describes a device or process that makes unauthorized access to the protected object easily detected. Seals, markings or other techniques may be tamper indicating
Titration	Also known as titrimetry, is a common laboratory method of quantitative chemical analysis that is used to determine the concentration of an identified component; the determination of rank or concentration of a solution with respect to water with a pH of 7 (the pH of pure H ₂ O under standard conditions)
USP (US Pharmacopoeia)	The United States Pharmacopeia (USP) is the official pharmacopeia of the United States, published dually with the National Formulary as the USP-NF. The United States Pharmacopeial Convention (usually also called the USP) is the nonprofit organization that owns the trademark and copyright to the USP-NF and publishes it every year. Prescription and over-the-counter medicines and other health care products sold in the United States are required to follow the standards in the USP-NF. USP also sets standards for food ingredients and dietary supplements
WTA (whole tobacco alkaloids)	A full-spectrum mixture of all alkaloids extracted from whole tobacco. WTA can contain, in addition to nicotine, anabasine, cotinine, myosmine, anatabine, and/or nornicotine, in varying compositions, largely dependent on the tobacco species

E-Liquid Manufacturing Standard

Article I. Verifying the accuracy of the nicotine content in products

Section 1.01 Accuracy of nicotine

- (a) All manufactures must confirm the accuracy of nicotine content upon delivery from supplier

Section 1.02 Titrated/verified after dilution

- (a) All nicotine must be titrated/verified for content accuracy after dilution to working level

Section 1.03 Measuring nicotine equipment

- (a) All equipment used in measuring nicotine from working level to final product must be either
 - (i) NIST (calibrated)
 - (ii) ASTM compliant (calibrated)

Section 1.04 Tolerance level

- (a) All products produced will be within the tolerance level of +/-10% nicotine content in final product

Section 1.05 Maximum allowable nicotine content

- (a) The maximum allowable nicotine content in final flavored product will be no greater than 36 mg / ml

Section 1.06 Retail nicotine sold for unflavored/DIY nicotine

- (a) Will follow the same criteria for verifying the nicotine content and quality on all batches when received and titrated after dilution at various sales levels
- (b) Is not subject to maximum allowable nicotine content in final flavored product

Article II. Ensure the quality and safety of the all ingredients of in e-liquid

Section 2.01 Nicotine Sources

- (a) All manufacturers must purchase and comply with at least one of the following:
 - (i) USP CERTIFIED nicotine (with evidentiary documentation from a certified lab)
 - (ii) Free-base nicotine from suppliers who can provide source evidentiary documentation from a certified lab confirming (batched) nicotine conforms to the Nicotine Quality Standard (see Section 2.02)
 - (iii) Purchase from nicotine suppliers who can provide evidentiary documentation from a certified lab confirming the incoming (batched) free-base nicotine conforms to the Nicotine Quality Standard (see Section 2.02)

Section 2.02 Nicotine Quality Standard

- (a) All nicotine used in manufacturing must meet the following nicotine quality standards:
 - (i) Nicotine purity greater than or equal to 99.0% *
 - (ii) Total combined of all other possible contaminants less than or equal to 1.0%
 - (iii) Per existence of any solvent must not exceed 0.06%
 - (iv) Per existence nicotine oxide less than or equal to 1%
 - (v) Per existence nicotine-N-oxides less than or equal to 1%
 - (vi) Cumulative heavy metals *content* cannot exceed 10ppm
 - (vii) Cumulative Arsenic *content* cannot exceed 1ppm
 - (viii) All diluents after source pure must be USP certified thru chain of custody

Section 2.03 Base liquid ingredients

- (a) Base liquid diluent ingredients such as Propylene Glycol, Vegetable Glycerin, Glycerol, or any other e-liquid bases (either regularly or exclusively) will be at a minimum level of USP (US Pharmacopoeia) grade certified
 - (i) Material must maintain full certification throughout chain of custody on raw materials used in manufacturing process
 - (ii) Manufacturer must exclusively use certified base products throughout the manufacturing process

Section 2.04 Ingredients/ Components other than base liquids

- (a) Ingredients/ Components other than base liquids will contain only safe or highest grade base materials
 - (i) Flavorings (including menthol) used will be at a minimum of food grade and/or Generally Recognized as Safe (GRAS) standard certifications whenever the ingredient is produced at those standards
 - (ii) Flavorings containing artificial food coloring will identify food coloring information to include coloring number in advertising and product descriptions
 - (iii) Flavorings containing Custard Notes will identify advertising and product descriptions
 - (iv) Water used (if any) will be either deionized or distilled
 - (v) Alcohol and additional additives (if any) will be:
 - 1) Used in the purest form commercially available and safe for human consumption
 - 2) Minimum of US Food grade standards

Section 2.05 The following will not be added or used in the creation of e-liquids

- (a) Including but not limited to:
 - (i) Diacetyl
 - (ii) WTA (whole tobacco alkaloids)
 - (iii) Medicinal - or prescription medicinal
 - (iv) Illegal or controlled substances
 - (v) Caffeine
 - (vi) Vitamins or Dietary supplements (other than for preservative purposes)
 - (vii) Artificial Food Coloring
 - (vii) Acetyl Propionyl (2,3-Pentanedione)

- 1) AEMSA members will not add any artificial coloring or dyes during the e-liquid manufacturing process. Non vendor manufactured flavorings containing artificial food coloring will identify food coloring information to include coloring number in advertising and product descriptions
- (viii) **AEMSA reserves the right to review, evaluate and deny/approve any potential substance used in the creation of e-liquids at any given time**

Section 2.06 Process/Records/Traceability

- (a) Manufactures will maintain sufficient process and records to enable the manufacturer to trace any individual product distributed to the test results for nicotine content to include source nicotine (see section 2.02)

Article III. Clean, Sanitary and Safe Preparation of Products

Section 3.01 General

- (a) All Lab/Mixing employees are required to be fully familiar with all AEMSA standards
 - (i) There will be a special emphasis placed on nicotine handling, storage and clean-up
- (b) Each member will create and maintain written lab/mixing protocol and make accessible to all lab/mixing employees
- (c) All Persons allowed in process area must comply with applicable protection/ safety and standards
- (d) All products will be created and/or bottled in dedicated manufacturing space reserved exclusively for e-liquid

Section 3.02 Manufacturing Environment

- (a) Manufacturing processes will meet food preparation standards to include
 - (i) Non-porous sanitized preparation work surface
- (b) All surfaces in lab/mixing area (floors, counters, etc.) shall be cleaned with anti-bacterial agents at least once each day and after any spill of any mixing ingredient or any possible-contaminants
- (c) Equipment will be cleaned by FDA Approved Chemical Sanitation or autoclave
- (d) All supplies and material will be disposed of in a manner that is appropriate to component disposal - proper disposal of production material
- (e) There shall be no open fans, dusty boxes and/or other potential sources of airborne contaminants etc. in dedicated space
- (f) All bottles and materials unpacked outside of dedicated lab/mixing space

Section 3.03 Hand washing / sanitation

- (a) Not in sink used for cleaning mixing utensils, and/or other e-liquid materials
- (b) Minimum 20 seconds with commercial (food handler's grade) antibacterial hand washing agent and warm water
- (c) Hands washed each and every time entering mixing room
- (d) After bathroom use, coughing, sneezing, eating and/or drinking, engaging in any other activities which potentially expose hands to any form of potential contaminants

- (e) During mixing as often as necessary to remove any mixing products on hands
- (f) Before proceeding to a subsequent mixing session -> to prevent any cross contamination from one batch to the next

Section 3.04 Health / illness

- (a) All open wounds or abrasion will be properly covered
- (b) Any/All mixing employees report any illness/abrasion(s)/lesions to person in charge before entering the process
- (c) Employees must report to person in charge if exposed to any contagion or infection - viral or bacterial - from anywhere (including others in their homes, other work environments, other domiciles, etc.) before entering lab/mixing area
 - (i) Such exposure/conditions excludes said individual from entering mixing room for a period of three (3) asymptomatic days have passed and/or cleared with medical documentation (equivalent to commercial food handling)
 - (ii) Discharge from eyes, nose and/or mouth:
 - (iii) Report to business any persistent discharge from eyes, nose, and/or mouth. Any employee exhibiting such symptoms shall not enter the mixing room until such symptoms cease

Section 3.05 Eating/Drinking

- (a) No eating, drinking, vaping and/or smoking in the lab/mixing area at any time

Section 3.06 Hair Restraints

- (a) Each member must establish written hair and beard standards

Section 3.07 Animals

- (a) No animals shall be permitted in the mixing room at any time for any reason

Section 3.08 POISONOUS OR TOXIC MATERIALS

- (a) POISONOUS OR TOXIC MATERIALS shall be stored so they cannot contaminate PRODUCT COMPONENT, FOOD, EQUIPMENT, UTENSILS, and SINGLE-USE ARTICLES by:
 - (i) Separating the POISONOUS OR TOXIC MATERIALS by spacing or partitioning
 - (ii) Locating the POISONOUS OR TOXIC MATERIALS in an area that is not above PRODUCT COMPONENTS, FOOD, EQUIPMENT, UTENSILS, or SINGLE-USE ARTICLES

- (iii) This does not apply to EQUIPMENT and UTENSIL cleaners and SANITIZERS that are stored in WAREWASHING areas for availability and convenience if the materials are stored to prevent contamination of PRODUCT COMPONENT, FOOD, EQUIPMENT, UTENSILS, LINENS, and SINGLE-SERVICE and SINGLE-USE ARTICLES
- (iv) All POISONOUS OR TOXIC MATERIALS will be disposed of in a safe manner
- (v) Only those POISONOUS OR TOXIC MATERIALS that are required for the operation and maintenance of a lab/mixing area, such as for the cleaning and SANITIZING of EQUIPMENT and UTENSILS and the control of insects and rodents, shall be allowed in a lab/mixing area (kept sealed and separate - never above - from any/all mixing supplies)
- (vi) A container previously used to store POISONOUS OR TOXIC MATERIALS may not be used to store, transport, or dispense any other substance

Section 3.09 Employee Safety

- (a) Employers MUST provide their employees with a workplace that does not have serious hazards and follow all relevant OSHA safety and health standards including - but not limited to - the following mandatory personal protective equipment (P.P.E.):
 - (i) Eye protection
 - (ii) Lab Coat / Apron
 - (iii) Fully covered footwear
 - (iv) All manufacturing spaces must have easily accessible
 - 1) First aid kit
 - 2) Emergency eye wash kit

Article IV. Safe Packaging and delivery of products

Section 4.01 Child proof caps

- (a) Child proof caps required for all consumer level e-liquid products
- (b) Zero Nicotine Products do not require child proof caps

Section 4.02 Tamper evident packaging

- (a) All Products require tamper evident packaging once leaving vendor chain of custody

Section 4.03 Labeling

- (a) Smear Resistant Labeling is required on all e-liquid products
 - (i) Must pass “30 second submerged” test for all required elements
- (b) Nicotine content must be clearly displayed
- (c) Safety and health Warning must be clearly displayed
 - (i) Contains Nicotine
 - (ii) Keep away from Children and Pets
- (d) Nicotine Traceability elements (i.e. Batch ID or nicotine batch ID or production date)

Section 4.04 Delivery

- (a) All shipped liquid must be bagged or wrapped to provide waterproof barrier between packaging and product for spill protection
- (b) Safe handling information must be included in all packaging

Section 4.05 Active age verification

- (a) All Vendors must use Active age verification for all sales (retail and/or online)
- (b) AMESA Members will not knowingly sell products to any persons under the legal smoking age

Article V. Transparency into the monitoring and verification process

Section 5.01 Within the organization

- (a) Members must provide information to applications and compliance committees required to establish compliance including:
 - (i) Documented evidence of compliance
 - 1) Photographic and Video evidence
 - 2) Unfettered access to facilities for inspection (scheduled and/or unscheduled)
 - 3) Process and records
- (b) Member to member profiles will contain only minimal information for the identification and communication amongst and between members
 - (i) Current status of compliance - by facility
 - (ii) Contact Information
 - 1) Name
 - 2) DBA
 - 3) Email
 - 4) Phone
 - 5) Location(s)/ Facilities of production

Section 5.02 To the consumer

Note: Subsections (a) and (b) are already posted on AEMSA website. Subsections (c) and (d) are intended for specific information warranted situations ONLY; these may include - but not limited to - allergy sensitivities, other specific medical conditions/sensitivities, etc. Subsection (e) shall be available on member's web site

- (a) A substantive version of the AEMSA Standards be published on Website
- (b) AEMSA Membership Status
- (c) ***Members will provide consumers tracking nicotine test results as far back as the source nicotine***
 - (i) ***Information on the supplier may be redacted to protect intellectual property and trade secrets***
 - (ii) ***The member may charge a reasonable and fair fee for said tracing requests***
- (d) ***Members will provide answers to consumers on ingredients of products***
 - (i) ***Yes/No answers to specific questions as pertains to specific customer sensitivity questions***
 - (ii) ***No intellectual property or trade secrets of the e-liquid ingredient has to be revealed***
 - 1) ***This includes revealing the source supplier and trademarked/brand name ingredient***
- (e) Clearly identified products that are not manufactured by AEMSA Members
 - 1) If the member sells liquid that is manufactured in a non AEMSA compliant facility it must:
 - 2) Clearly identify/ differentiate products that are AEMSA compliant and those that are not AEMSA compliant on a product by product basis

Section 5.03 To potential regulators

- (a) To be decided on case by case basis